**DRUGS *and* PREGNANCY**

* **INTRODUCTION**
  + Uterus important organ for child birth—houses the developing egg, embryo and fetus and interfaces with the placenta
  + Uterus wall composed of smooth muscle
  + Uterine smooth muscle plays important and complex roles in the birth process
    - Effacement-- opening up and becoming more elastic
    - Contractions of wall—important in pushing baby out
    - Involution-- must return to its original state so it can start the process all over again
  + In some patients it is necessary to induce labor and in other patients to delay labor

**UTERINE STIMULANTS (OXYTOCICS)**

* Drugs that contract uterine smooth muscle
  + Increase motility and contraction of the uterus
* **PROSTAGLANDINS**
  + Autacoids produced in many tissues
    - Key enzyme is cyclooxygenase (types 1 and 2)
    - Blocked by NSAIDs
    - Short plasma half-life ~ 2.5-5 min—so they have local effects
  + **PGE2 and PGF2alpha** induce contraction of uterine SM during pregnancy
    - Synthesis by uterus increases at term
      * Especially during the end of the pregnancy
    - Levels in maternal blood, umbilical blood and amniotic fluid increase at term and during labor
    - Synthesis and effects inhibited by progesterone (inhibits the production)
  + **CERVICAL RIPENING prior to labor induction**
    - **PROSTAGLANDIN E2 (PGE2)**
      * ***In cervix:*** Relaxes SM and stimulates release of collagenase, which breaks down the collagen that makes cervix rigid—so it breaks down the collagen which makes the cervix more soft and elastic—CERVICAL RIPENING
      * ***In uterine wall:*** Induces contractions
        + Augments oxytocin effects, therefore, therapy should be stopped prior to administration of oxytocin
      * Shortens time to onset of labor and delivery time
    - **SIDE EFFECTS**
      * Increases GI motility → nausea, vomiting, diarrhea
        + Same side effects as all of the other prostaglandins
      * Hyperstimulation of uterus SM—which is undesirable
    - **PREPARATIONS FOR CERVICAL RIPENING**
      * **DINOPROSTONE (PGE2)—cervical ripening and induces contractions**
        + *Prepidil*® (1992), endocervical gel, 0.5 mg PGE2

Administered via cervical catheter and syringe

Length of catheter depends on the amount of effacement that has occurred once it is in there you cant get it out so it can have a prolonged effect (can last up to 12 hours)

20 mm or 10 mm catheter with 0 or 50% effacement

Often requires 2 doses, 6 hours apart

Oxytocin may be administered **6-12 hr** after last dose

Oxytocin is used to induce labor

Wait this much time before you induce the labor with oxytocin

* + - * + *Cervidil*® (1995), retrievable, vaginal insert w/ string to remove it

Contains 10 mg PGE2 released at 0.3 mg/hr for 12 h

Oxytocin may be administered **30 min** after removal

Once you remove it you remove it's effects so you can stimulates labor

Remove if active labor begins

Remove if hyperstimulation (5%) or fetal distress

The string allows quick removal if you have these side effects

* + - * **MISOPROSTOL** (*Cytotec*®, 1988)—cheaper than dinoprostone
        + A tablet that can provide prostaglandins to help the stomach protected from acids and also cervical ripening

Help counteract the adverse effects of NSAIDs on the GI tract.

* + - * + PGE1 derivative, alternative to dinoprostone, but not FDA approved – “off-label” use
        + ¼ 100 mg tablet inserted vaginally every 4 h

If you cut it up and insert it vaginally then you get the same effects as dinoprostone

* + - * + ADVANTAGES

More effective, works faster, less need for oxytocin

More convenient, stored at room temp because they are dry tablets

Much less expensive $1 ***versus*** $175 for *Cervidil®* and potentially 3x $150 for *Prepidil*®

* + - * + DISADVANTAGES

Higher incidence of uterine hyperstimulation

* + **INHIBITION of POST-PARTUM BLEEDING (placental delivery)--↓ post partum blood loss**
    - **CARBOPROST** (15-Me-PGF2a, *Hemabate*®, ’79)
      * PGF2α derivative
      * Used when oxytocin or methylergonovine fail to work—It is a third line drug
        + Single IM dose (250 mg) usually sufficient (max dose 2 mg)

injected IM so you have more systemic effects and side effects

* + - * MECHANISM:
        + Contraction of uterine SM most important (will compress the BV’s in its wall), but
        + Also causes vasoconstriction (PGF2a) so will decrease the blood loss
      * ADVERSE EFFECTS
        + GI effects, nausea, vomiting, diarrhea 60% patients-- especially since it's a systemic drug

Can pretreat with antiemetic and antidiarrheal

* + - * + Fever is common-- when it gets to the brain
        + Systemic Vasoconstriction can → BP↑, bronchoconstriction (PGF2a)
  + **TERMINATION OF PREGNANCY**: PROSTAGLANDINS –b/c induce contraction of uterine SM
    - For abortion of early pregnancy
      * **MISOPROSTOL** (PGE1 analog) (oral)
        + Approved for use withtheantiprogestin **MIFEPRISTONE** (RU486, *Mifeprex®*),toinduce abortion up to 49th day of gestation (3x200 mg RU486 + 2x200 mg oral PG)

Mifepristone blocks the progesterone and embryo becomes detached and misoprostol induces contractions to expel the embryo

Misoprostol can be used 2-3 days later for SM contractions

* + - For 2nd trimester abortion (wks 12/13-20)
      * **DINOPROSTONE**(PGE2, *Prostin E2®* 1977)
        + Vaginal suppository, 20 mg every 3-5 hours as needed
      * **CARBOPROST** (15-Me-PGF2a) (*Hemabate*®, 1979)
        + IM injection, 250 mg every 1.5-3.5 h as needed
      * Mean time to abortion is 17 hr, but 25% incomplete
* **OXYTOCIN**
  + Natural peptide hormone
  + Principle use **- induction of labor**
  + POSTERIOR PITUITARY HORMONES
    - Posterior pituitary secretes two peptide hormones-- peptide hormones with disulfide bridges
      * Vasopressin (antidiuretic hormone)
      * Oxytocin
    - Synthesized in neurons in hypothalamus
    - Stored in secretory granules in nerve endings in posterior pituitary until released into circulation
  + **OXYTOCIN** (*Pitocin*®, 1980)
    - MECHANISM in UTERUS
      * G protein-linked memberane receptors (similar to V1 for vasopressin) linked to elevation of Ca2+ in uterine smooth muscle and causes contraction
      * Increases local uterine prostaglandin production towards the end of gestation especially
    - ADMINISTRATION
      * IV, IM or nasal spray
      * **Inactive** if given orally
    - Plasma half-life short ~12-15 min—Vasopressin also has short half life. The short half life allows the effect to go away quickly and allows you to adjust rate of infusion when it is given IV
      * Metabolized in liver and kidney
    - ACTIONS
      * Increases force, frequency and duration of uterine SM contraction, with normal relaxation
        + Sensitivity starts low, but increases throughout pregnancy

During pregnancy, number of receptors increases 30x

Not essential for delivery but it seems it is very useful

Just before term, there is an abrupt large increase

* + - * + Physiological role in delivery uncertain - it is not essential
      * Contracts myoepithelial cells surrounding mammary alveoli in the breast, needed to eject milk into the sinuses
        + Reflex arch--Suckling induces a neuronal reflex that releases oxytocin
      * Has weak antidiuretic and vasopressor activity
        + Acts at vasopressin (ADH) V2 and V1 receptors in the collecting duct of the kidney and causes water retention and hyponatremia
    - OXYTOCIN: USES
      * INDUCTION OF LABOR (~20% of deliveries involve induction of labor) – ***when do you induce laboor?***
        + Pregnancy has continued **beyond term** - 42 weeks

40 weeks is the standard term for pregnancy

* + - * + When **early** vaginal delivery will decrease mortality or morbidity for mother or baby, i.e. **when continued pregnancy is a greater risk than the induction**

Premature rupture of amniotic membranes - *most common reason*

Decreases the risk of infections

Severe maternal infection

Diabetes mellitus

Placental insufficiency

Renal insufficiency

Anemia

Pre-eclampsia (at or near term, discussed later)

* + - * + Induction simply for convenience is controversial (2/3)-- 2/3 of deliveries are done for convenience not necessity
      * Oxytocin use for induction of labor is contraindicated (use a caesarian section in these situations!)
        + Cephalopelvic disproportion—when the head is bigger than the gap in the pelvis for the baby to fit through
        + Placental abnormality
        + Abnormal fetal presentation
        + Umbilical prolapse
        + Previous uterine surgery
        + Fetal distress
        + Improper use of oxytocin can lead to rupture of uterus and death of mother and/or fetus
    - PREINDUCTION
      * Before induction is begun, fetal lungs must be sufficiently mature and the cervix ripe (cervix must be ripened!!!!)
        + Glucocorticoids
        + Prostaglandins
    - INDUCTION – Oxytocin ADMINISTRATION
      * Dilute solution (10 mU/ml) via IV infusion pump (continuous)
      * Rate increased slowly from 6 mU/min until physiol. contraction pattern is established - max 40 mU/min
      * ***Maternal Monitoring:*** BP, HR and uterine contraction
        + Stop infusion if resting uterine pressure > 15-20 mmHg

If it goes above this then slow down infusion

* + - * + Stop infusion if contraction duration > 1 min

The baby doesn't receive blood flow with each contraction so these must be short

* + - * + Stop infusion if contraction frequency > 1 per 2-3 min
      * ***Fetal Monitoring:*** HR and rhythm
        + Stop infusion if heart rate or rhythm become abnormal
      * Response to change in infusion rate is rapid - ***why?*** B/c oxytocin has such a short half life
    - OTHER USES
      * Augmentation of dysfunctional labor
      * Control of post-partum uterine hemorrhage
        + After delivery of placenta, 10 U IM, or
        + 10-40U in 1 L of 5% dextrose infused 10 ml/min
      * Promotion of milk ejection--effects on the myoepithelial cells in the breast they can inhale it into the nose before feeding and it can help promote milk ejection
        + One puff into each nostril, 2-3 min before nursing
      * ***Oxytocin Challenge Test*** – Uterine contractions stop the flow of blood through the placenta and limits the blood supply to the fetus and this is a stress on the fetus and maybe the placenta isn’t working well enough to maintain supply of oxygen to the fetus.
        + Administered IV oxytocin near term to produce uterine contractions (3 contractions in 10 minutes) that temporarily cause the fetal blood supply ↓
        + If fetus healthy, no change in heart rate
        + If fetus not healthy, oxygen deficiency → fetal HR ↓--might want to perform a C-section instead of a normal delivery
    - OXYTOCIN: TOXICITY
      * Serious toxicity is rare, *but includes*
      * Uterine rupture—can occur from excessive contractions
        + Maternal and/or fetal death
      * Water intoxication, rare - ADH effect (can activate the ADH receptors V1)
        + Most likely when oxytocin is administered in a large volume—can lead to ↑ water retention
        + Can cause convulsions (caused by hyponatremia), coma and even death
* **ERGOT ALKALOIDS--** **older drugs used for hundreds or thousands of years**
  + A fascinating group of drugs produced by *Claviceps purpurea,* a fungus that grows on grains, especially rye
  + Like LSD are derivatives of **LYSERGIC ACID**
  + ***Ergotism***: effects of ergot poisoning
  + **ERGOT POISONING**
    - Consumption of contaminated grain leads to ergotism or “*St. Anthony’s Fire*”-- back in the middle ages
      * Dementia with florid hallucinations--LSD like effects
      * **VERY Prolonged** vasospasm/vasoconstriction → ischemic pain/“fire” and gangrene of feet, legs, hands and arms
        + Turned black and dropped off and looked like it burned from St. Anthony's fire
        + The reason for prolonged effects is very tight binding of the compound to the receptor
      * Uterine smooth muscle contraction → spontaneous abortion
    - MECHANISM: Contains 20 different ergot compounds including agonists, partial agonists and antagonists at
      * α-adrenergic receptors
      * Dopamine receptors
      * Serotonin (5-HT) receptors (5-HT1A, 5-HT1D, 5-HT2)
  + Ergot compounds are divided into 2 groups
    - ***Amine ergot alkaloids***, e.g. **ERGONOVINE** first purified in 1932
      * Important for effects on uterus
      * Rapid GI absorption and rapid metabolism
    - ***Peptide ergot alkaloids***, e.g. **ERGOTAMINE** first purified in 1920
      * Important in treatment of **hyperprolactinemia** and also **migraine**
      * Poor GI absorption, bioavailability <1%, slower metabolism, - longer duration of action
  + ***AMINE* ERGOT ALKALOIDS**
    - Ergonovine, methylergonovine and lysergic acid diethylamide (LSD)
    - Rapid GI absorption and metabolism—good bioavailability
    - **ERGONOVINE**, (*Ergotrate*®, ?) **METHYLERGONOVINE** (*Methergine*®, 1946)
      * MECHANISM
        + Partial α-adrenergic agonist on SM
        + Partial 5-HT2 agonist on SM

Causes contraction of the uterus via these 2 receptors

Difference between oxytocin is that amine ergot alkaloids are less physiological

During a normal contraction you have it followed by relaxation but with these drugs you can get the normal pattern of contraction at low doses but at high doses you end up with a continuous contraction (not good for fetus)

* + - * ACTIONS on UTERUS
        + Contraction strong and prolonged--a continuous contraction and not a relaxed period in between (\*bad)
        + Sensitivity increases as pregnancy progresses
        + Low doses increase force and frequency of contractions with **normal relaxation,** alsovasoconstriction
        + As dose is raised, force increases and **resting tone increases,** sustained contraction can result
      * USES/INDICATIONS
        + In 18th century, **Ergot** was used to accelerate labor, but led to increased maternal and fetal mortality (1824)
        + Second stage of labor - following delivery of anterior shoulder - but, only with full obstetric supervision
        + **Primarily** used **postpartum** now, **METHYLERGONOVINE**

***Routinely*** used to assist involution and decrease hemorrhage

Uterus shrinking back to its original size

***Treatment*** of subinvolution of uterus and atony

***Treatment*** of postpartum hemorrhage--NUMBER 1 REASON!!

* + - * ADMINISTRATION
        + Usually administered after placenta delivered

Oral tablet - effects seen in 5-10 min, peak plasma conc ~ 1 hr

IM injection - effects seen in 2-5 min

IV injection - effects immediate, but… (not recommended – due to BP↑)--must give it slowly bc it causes the vasoconstriction and the BP just goes up

Use is limited to a **maximum of 1 week *– why?*** B/c they have a very long effect and the vasoconstriction accumulates

* + - * BIOAVAILABILITY – ***contrast ergotamine***
        + Methylergonovine oral ~60%, IM ~80%
      * ADVERSE EFFECTS – rare with IM or oral
        + Amine ergot alkaloids **less toxic** than **peptide** alkaloids
        + Hypertension – most common, frequent when IV

In some cases, associated with seizure and/or headache

Do not use in hypertensive patients

* + - * + Nausea and vomiting (CTZ, GI) – 10%

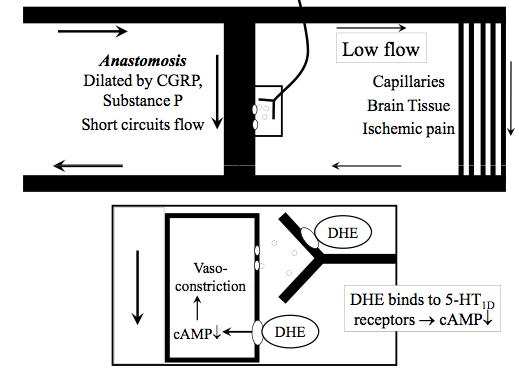
D2 agonists causes vomiting!!

* + - * + Numbness, tingling of fingers and toes-- excessive vasoconstriction
        + Overdose/prolonged use can lead to “ergotism”

Above symptoms, ***plus:*** respiratory depression, hypothermia, convulsions, coma-- so much vasoconstriction!!!

Prolonged vasospasm, which may lead to gangrene and require limb amputation

**KEY DRUGS FOR MIGRAINES**

* ***PEPTIDE* ERGOT ALKALOIDS🡪 ERGOTAMINE/DIHYDROERGOTAMINE**🡨 Only difference between these 2 drugs is that Dihydro has the double bond reduced
  + Similar in structure to the AMINE ERGOT ALKALOIDS except that it has amino acids stuck on the end and they are less lipophillic and are not absorbed as readily
  + **ERGOTAMINE** (purified in 1920), **DHE** and **BROMOCRIPTINE**
  + Poor GI absorption and low oral bioavailability
  + **TREATMENT of MIGRAINE-- ERGOTAMINE/DIHYDROERGOTAMINE (DHE)**
    - Only difference between these 2 drugs is that DHE has the double bond reduced
    - **Used for acute treatment** of migraine headaches (with or without aura – visual effects) and cluster headaches
    - Most useful if given during the “prodrome”
    - ACTIONS/MECHANISM (?)
      * Partial a-adrenergic agonist (Ca2+↑)
      * Partial 5-HT2A, 5-HT2C agonist vascular s.m. (Ca2+↑)
      * Also D2 and D3-dopaminergic agonist (cAMP↓)
      * Agonist at presynaptic **5-HT1D** receptors (cAMP↓) on ***trigeminal nerves*** innervating cranial blood vessels
        + Inhibits release of inflammatory/vasodilator peptides, e.g. CGRP (calcitonin gene related peptide), substance P
      * Agonist at cranial vascular s.m. 5-HT1D receptors, e.g. on arterio-venous anastomoses
      * Should not be used prophylactically or prevention JUST DURING ACUTE ATTACK or when they have a prodrome and feel a migraine coming on.
      * ***MECHANISM***: Dihydroergotamine
        + This is blood flow to the brain—the brain gets the blood and uses the O2 and then it drains off on the venous side. So you have these anastomosis that are kind of short circuits that allows some of the blood to go into the venous circulation before it gets into the brain. Then there are these neurons that release things like calcitonin gene related peptide (CGRP) and sub P and these cause vasodilation of the anastomoses and they trigger inflammation which may trigger more stimulation and more release. When you have dilation of the short circuit you get ischemia (in the area on the R in the picture above), which leads to pain. So to prevent this you need to constrict the anastomosis to promote blood flow in the area on the R. And we do this by using DHE binding to the 5-HT1D receptors which are coupled to a Gi protein which ↓ cAMP and when you ↓ cAMP in vascular SM you cause constriction. There are also presynaptic 5-HT1D receptors and if you remember when there is an ↑ cAMP in the nerve terminal it stimulates release of neurotransmitter and when ↓ cAMP you inhibit it—so here we are inhibiting the release of the substances that are causing vasodilation (CGRP, Sub P)
    - ***BIOAVAILABILITY*** very low – first pass metabolism
      * Often combined with caffeine (vasoconstrictor in the brain) said to increase rate and extent GI absorption, but bioavailability still ~ 1%
      * Administered oral, sublingual, rectal, nasal, IV, IM
      * **ERGOTAMINE**
        + *Ergomar*®, generic ’83, **sublingual**
        + *Cafergot*®, 1953, **rectal suppositories**, with 100 mg caffeine
        + *Ercatab*®, oral tabs, with caffeine
        + \* various routes!! also given with caffeine which is also a vasoconstrictor in the brain
      * **DIHYDROERGOTAMINE**
        + *D.H.E.45®*, 1946, IV, SC or IM injection
        + *Migranal*®, 1997, nasal spray with caffeine
    - HALF-LIFE of DHE ~ 9-10 hr
    - ADVERSE EFFECTS - ***IMPORTANT***
      * Nausea/vomiting (10% oral, 20% parenteral, E>DHE)—D2 receptors
        + Metoclopramide often used as adjunct - ***Why?***
        + Try to establish maximum, sub-nauseating dose
      * Potent vasoconstrictor with prolonged action - difficult to reverse due to tight binding (E>DHE)
        + Numbness, tingling of fingers and toes
        + Hypertension
        + Coronary vasospasm
        + Cumulative vasoconstriction occurs with each dose
        + Should not be used during pregnancy because it vasoconstricts and causes contraction the uterus!!!
        + ***Consequence:*** Limit dose to 6 mg/attack or 10 mg/week
    - CONTRAINDICATIONS
      * Patients with CAD, Peripheral Artery Disease, hypertension ***or*** at risk of CAD, (i.e. if BP↑, cholesterol↑, diabetes, obese, post-menopausal women, men > 40 y/o, family history)
      * Pregnancy cat. X → fetal distress, toxicity due to decreased utero-placental blood flow
      * Hemiplegic or basilar migraine
    - DRUG INTERACTIONS - CYP3A4 INHIBITORS
      * ***Black-Box warning:*** Ritonavir, erythromycin, etc. can elevate plasma **DHE** b/c they inhibit CYP3A4 which metabolizes DHE→ serious or life-threatening cerebral or peripheral ischemia
* **“TRIPTANS”—more selective for 5-HT1D  receptors than ergotamine**
  + First line drugs for migraine with or without aura
    - **Sumatriptan** (*Imitrex*®, 1992, SC, oral, nasal)
    - Zolmitriptan (*Zomig*®, 1997)
    - Naratriptan (*Amerge*®, 1998)
    - Rizatriptan (*Maxalt*®, 1998)
    - Almotriptan (*Axert*®, 2001)
    - Frovatriptan (*Frova*®, 2001)
    - Eletriptan (*Relpax*®, 2002)
  + **SUMATRIPTAN** (*Imitrex*®, 1992)
    - Selective agonist at 5-HT1D (and 5-HT1B) receptors on ***cranial*** vascular SM and presynaptic membranes
      * These drugs are more selective
        + They are not working at the α receptors or 5-HT2 receptors like ergotamine and DHE do
    - Little effect on arterial BP, or PVR
    - First-line therapy for **ACUTE** severe migraine
      * **NOT** for prophylactic therapy because you can't use these chronically
        + You take them when you feel a migraine coming on
      * Second dose can be taken after 2 hr (t½ ~ 2 hr)
      * Maximum oral dose **limited** to 200 mg in a day
    - Oral bioavailability 15% - first-pass effect
      * Metabolized by MAO-A
        + So drug interactions with MAO Inhibitors
      * SC, oral and nasal preps available
    - Half-life = 2.5 hr
    - Drug Interactions
      * MAO-Is, **SSRIs (serotonin antagonists--*serotonin syndrome* life threatening)**, ergot derivatives
        + MAO inhibitors- Selegelline and Tranylcypromine
        + If you combine MAO-I w/ SSRI’s you block metabolism of serotonin (done by MAO) and you block uptake (SSRI) so you get excessive actions of serotonin
    - Pregnancy category C - avoid use
      * In rats and rabbits, produces embryolethality, fetal abnormalities, and pup mortality
        + Not shown to cause problems in women but found to in animals
    - ADVERSE EFFECTS – most are transient and mild
      * **Most common** (50%) – unpleasant chest symptoms - described as “heavy arms” and “chest pressure”
        + Patients should be warned and told it is not dangerous
        + Possible causes

Pulmonary vasoconstriction, esophageal spasm, intercostal muscle spasm, bronchoconstriction—not sure exactly what is causing these symptoms tho

* + - * Vasospasm of arteries (heart, brain, GI)-- not much usually involved with the peripheral but they can cause some problems
        + **Biggest concern** – coronary vasospasm
        + **Contraindicated** in patients with CAD

Not recommended for patients at risk of CAD, e.g. post-menopausal women, men > 40 y/o, BP↑, cholesterol↑

* + - USE of SUMATRIPTAN ***vs*** DHE
      * Sumatriptan works faster in providing relief attacks so this is very useful because want to stop a migraine as fast as possible
        + Effects seen

In 15 min after SC administration

In 30-60 min after oral administration

* + - * + Complete relief in 2 hr for 70-80% patients
        + But, 40% patients headache returns within 48 hr
      * DHE has lower recurrence rate
        + Effects seen in 2 hours?
        + Only 18% migraine recurrence within 24 hr
      * ***Both*** contraindicated in patients with CAD
* **LYSERGIC ACID DIETHYLAMIDE (LSD)**
  + Synthetic derivative of ergot compound lysergic acid
  + Potent hallucinogen – *mechanism uncertain*
    - Agonist at pre- or post-junctional 5-HT2 receptors in CNS or 5-HT1A and 5-HT1C
    - Lysergic acid itself is inactive
  + ***Schedule 1*** controlled substance
    - i.e. ***no*** approved clinical uses
  + See “*Drug Abuse*” notes for further information

**DRUGS USED TO TREAT INFERTILITY CAUSED BY HYPERPROLACTINEMIA**

* **BROMOCRIPTINE** (*Parlodel*®, 1978)
  + Fairly Selective D2 agonist (cAMP↓)
  + USES
    - **Hyperprolactinemia - lowers plasma prolactin** 
      * Dopamine inhibits release of prolactin from the anterior pituitary--very effective
        + Dopamine antagonists actually cause hyperprolactinemia
    - Acromegaly – caused by ↑ GH so this drug lowers plasma growth hormone 50% in these patients also acts in the anterior pituitary
    - Parkinson’s disease – acts in *c. striatum*
    - **HYPERPROLACTINEMIA**
      * Occurs secondary to anterior pituitary adenomas (secreting prolactin—prolactinoma)
      * PROLACTIN
        + Polypeptide hormone produced by anterior pituitary
        + Stimulates ***milk production*** after parturition

Different from oxytocin—which promotes milk ejection

* + - * + Prolactin secretion

Normally inhibited by dopamine (D2, cAMP↓) released from neurons from hypothalamus

Stimulated by suckling—reflex arch

* + - * Effects of hyperprolactinemia
        + ***Women***: Galactorrhea, amenorrhea, **infertility** (interferes with normal fertility and ovulation)- mechanism unknown
        + ***Men***: Impotence and sometimes galactorrhea
      * Treatment of hyperprolactinemia and associated infertility
        + Bromocriptine suppresses prolactin release

Reinstates normal ovulatory menstrual cycles and restores fertility, takes few days - 2 months

Suppresses galactorrhea (excess milk production)

Continuous tx can induce **regression of the tumor**, sometimes for years

* + - * + Therapy should be stopped as soon as patient becomes pregnant and not resumed till after delivery

Especially if patient has PIH (pregnancy induced hypertension) or develops pre-eclampsia

* + SIDE EFFECTS
    - Hyperprolactinemia patients
    - **Nausea (50%)/vomiting (works at the chemoreceptor trigger zone) and other GI symptoms, headache (19%), dizziness (17%)** sometimesorthostatic hypotension
      * Remember it's a D2 agonist
      * Antiemetics can be D2 antagonists
  + ADMINISTRATION
    - With food to minimize nausea/vomiting
      * 2.5 mg, 2-3x/day
* **Other Ergot D2 Agonists**
  + PERGOLIDE (*Permax*®, 1988-2007)
    - USE - Parkinson’s disease - adjunct to levodopa
    - More potent than bromocriptine
    - Removed from market because heart valve damage
  + CABERGOLINE (*Dostinex*®, 1996)
    - USE – Hyperprolactinemia –dose lower than for Parkinsons Disease so ↓ risk for heart valve disease
    - Long half-life = 63-69 hr, administered 2x/week
    - Side effects, nausea, constipation, headache

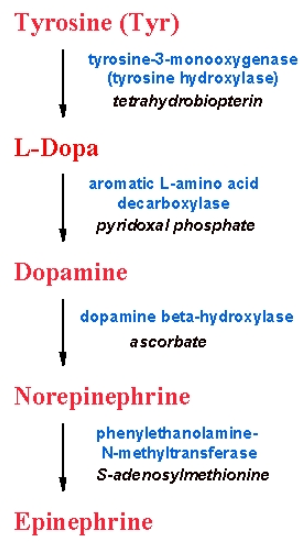
**UTERINE RELAXANTS (TOCOLYTICS)—ending of labor**

* Relax the uterus, unlike the others we talked about that stimulate the uterus to contract and start labor process
* Drugs used to suppress premature labor and birth
  + Inhibit contraction of the uterus
* PREMATURE LABOR/BIRTH
  + Premature birth defined as < 37 weeks gestation
  + In USA, 11% births are premature
  + Leading cause of infant morbidity and neonatal mortality in USA
    - Most common complication of early birth: ***neonatal respiratory distress syndrome* – Why?** Because lung development occurs later in utero
    - Respiratory system is last fetal system to mature
  + Tocolytics can suppress labor, but average delivery delay is only 48 hr – ***so why bother?*** **WINDOW FOR SURFACTANT DEVELOPMENT!!!**
    - *Answer:* Allows use of **glucocorticoids** to ***accelerate fetal lung development***
* **RESPIRATORY DISTRESS SYNDROME (RDS)**
  + RDS results from deficiency of lung ***surfactant***
    - A mixture of phospholipids (PC) and apoproteins that lowers the alveolar surface tension which prevents the alveoli from collapsing
  + Without sufficient surfactant:
    - Alveolar collapse, pulmonary edema
    - Lung compliance↓, small airway epithelial damage
    - Hypoxia and ultimately respiratory failure
  + Hydrocortisone ***initiates*** surfactant/lecithin synthesis in wks 30-32, becomes ***adequate*** in wks 34-36
    - Result: delivery at 26-28 wks 60-80% RDS  
       delivery at 30-32 wks only 20% RDS
  + PREVENTION
    - Glucocorticoids administered to mother are beneficial when given between weeks 24-34
    - MECHANISM
      * GCs stimulate synthesis of ***fibroblast pneumocyte factor***, that stimulates surfactant production by type II pneumocytes and stimulates lung maturation
    - Two regimens-- work on the **type II pneumocytes**
      * **DEXAMETHASONE** (*Decadron*®)
        + Four 6 mg IM, 12 hours apart
      * **BETAMETHASONE** (*Celestone*®)
        + Two 12 mg IM, 24 hours apart
    - Last dose should be administered >24 hr before, but <7 day before delivery-repeat courses should be avoided
      * These drugs work on protein synthesis, they don't have immediate effects. You need delivery to occur 24 hrs🡪 7 days after last dose of glucocorticoid was given
* **MAGNESIUM SULFATE (MgSO4)**
  + Tocolytic **DRUG OF CHOICE**, because has lowest risk of side effects and low cost, while efficacy is similar to other tocolytics
    - So slowing down labor efficacy, low cost, low risk -good drug
  + MECHANISM - a Ca2+ antagonist? Mg pretty much competes w/Ca and we know Ca is involved in regulating almost everything especially SM contraction and NT release, heart activity, respiration, etc. It is tricky to block Ca without having significant side effects
    - Normal [Mg2+]plasma 1.5-2 mM, but at 4-7 mM inhibits **ACh release** at **uterine** neuromuscular junctions
      * Blocks Ca entering the nerve terminal to release the vesicles of NT
        + normal NT release involves Ca entering the nerve terminal and releases the vesicles
      * ACh is responsible for the contraction of uterine SM
    - Concentrations > 7 mM inhibit **skeletal** muscle NMJs → weakness → trouble w/ respiratory & cardiac arrest
      * Narrow therapeutic range
  + ELIMINATION: 100% by kidney
    - Remember 70% normally reabsorbed in the Thick Ascending Limb (TAL)
  + ADMINISTRATION - IV infusion pump
    - Bolus 4-6 g, then infusion 2-3 g/hr for 48-72 hr
      * Bolus then infusion = Loading dose = big dose given at the beginning to get the concentration up quickly. Woman is going into labor and so you don't have days to get this drug up to the level you want it at in the blood
  + ADVERSE EFFECTS
    - ***In therapeutic range:*** Usually well-tolerated
      * Initial transient **HYPOTENSION** (flushing, headache, dizziness, feeling of warmth), dry mouth
    - **Pulmonary edema** (2%), can be fatal (MAIN PROBLEM!!!)
      * Accumulation of fluid in the lung
      * Cease infusion and administer a diuretic to increase excretion of Mg2+ and fluid
    - ***Higher doses:*** Flushing, hypothermia, paralytic ileus
    - ***Toxic levels:*** Somnolence, hypotension, paralysis, respiratory depression, cardiac arrest
  + MONITOR - to reduce risk of adverse effects and make sure levels stay in the right range
    - **Mg2+ levels** every 4 hr
    - **Deep tendon reflexes**: loss of reflex is an early indicator that Mg2+ levels are dangerously high (at 10 mmol you have no reflexes at all—so stop infusion until reflexes return)
      * Reflex response is very sensitive response that is a good indicator of Mg.
    - **Renal function** and fluid balance – This is the way the body eliminates the Mg. So you need to use it to detect fluid retention which increases risk of ***pulmonary edema***
  + CONTRAINDICATIONS
    - Myasthenia gravis-- antibodies against the nicotinic Ach receptors so you get weakness and inability of muscles to contract. So adding Mg to further reduce muscle contraction is not desirable.
    - Renal failure—this is how we get rid of the Mg
    - Hypocalcemia - intensifies effect of Mg2+
  + TREATMENT of TOXICITY
    - Calcium gluconate (oxidized form of glucose), administered IV
  + EFFECTS on NEONATE
    - Mg2+ readily crosses placenta
    - Newborn may suffer-- with too much Mg
      * Muscle weakness (hypotonia)-- signs of too much Mg—suppression of nerve function
      * Sleepiness
    - Effects may persist for several days – ***Why?***
      * Newborn kidney function not fully developed – GFR neonate 30-40% of adult. So takes longer to get rid of the Mg
* **β2-SELECTIVE ADRENERGIC AGONISTS—were important class of drugs for asthma** 
  + Terbutaline (*Brethine®*)-- also used for asthma, etc.
  + Ritodrine (*Yutopar®*)-- was the only β2 agonist for inhibiting labor but it's not on the market anymore
  + **TERBUTALINE** (*Brethine®,* 1974) and **RITODRINE**
    - Selective for β2-receptors
    - Major Uses: FDA update 2-2011:
      * Tocolysis(?)- Delay onset of labor wks 20-36 (IV, oral)
        + Initial IV infusion for max of 48-72 hrs only in hospital setting, oral administration contraindicated-- can only use 2-3 days max to stop pregnancy
      * Prophylaxis and treatment of acute asthma attack
    - Administration
      * **IV, and oral**
      * Side effects: Cardiac stimulation β1 or β2 action → death, etc.
        + This drug isn't in good shape either-- cardiac problems
        + So not being used anymore. FDA is pushing that these be avoided
* **Ca2+ CHANNEL BLOCKERS**
  + **NIFEDIPINE**
    - Blocks Ca2+ channels in smooth muscle, including uterus, vascular system arterioles
    - Can suppress labor for at least 48 hr to allow treatment w/ glucocorticoid for fetal lung development
    - Maternal side effects from vasodilation
      * Tachycardia, hypotension, facial flushing, headache, dizziness, nausea-- all result from lowered blood pressure and vasodilation
      * Hypotension may occur in hypovolemic patients
        + May compromise uteroplacental blood flow

Dropping maternal blood pressure makes you worry that the fetus isn't receiving enough blood (which carries nutrients and oxygen to the fetus)

* + - ADMINISTRATION
      * 5-10 mg sublingual every 15-20 min,  
         then 10-20 mg oral every 4-6 hours
* NSAIDS: **INDOMETHACIN**
  + **Second-line** tocolytic drug, used when other drugs are ineffective and if ***< 32 weeks***(b/c it can also cause premature close of the ductus arteriosis in the fetus)
  + Blocks uterine PG synthesis
  + Administration:
    - Rectal 50-100 mg, followed by oral 25-50 mg/6h for 2-3 days
    - Short period of use to slow down labor
  + Maternal adverse effects
    - Nausea, gastric irritation
    - Interstitial nephritis
    - Increased post-partum bleeding
      * b/c platelets use thromboxane which needs COX to synthesize it to promote platelet aggregation and clotting. So when you take NSAIDS you ↓ the ability to clot thus promoting bleeding.
  + Neonatal adverse effects- These are pretty bad effects so not a first line drug!!!
    - Renal failure
    - Broncho-pulmonary dysplasia
    - Respiratory distress syndrome
    - Premature closure of the *ductus arteriosus*, especially if used after 32 wks gestation
    - Necrotizing enterocolitis
    - Intracerebral hemorrhage
  + ***Reminder:*** Other uses - closure of ductus arteriosus, and acute gouty arthritis
* **HYDROXYPROGESTERONE** Caproate (*Makena*®, 2011)
  + INDICATION
    - Reduce risk of preterm birth in women with a history of preterm birth – ***not for use in active labor***
  + ADMINISTRATION: IM injection 1/week beginning at weeks 16-21 until week 37 (when delivery is acceptable)—thought is that by its normal action of progestin it will delay that premature birth
  + MECHANISM – unknown
    - Progesterone levels decline at labor in some species
    - Progesterone administration inhibits secretion of pro-inflammatory cytokines and delays cervical ripening

**HYPERTENSION in PREGNANCY**

* Common in pregnancy ~10% of patients who are pregnant have hypertension
  + Chronic “essential” hypertension ~5%
    - Present before pregnancy or before 20th week
    - They were treated for hypertension before they got pregnant or they develop HTN early in preg.
  + Pre-eclampsia (PIH) and eclampsia—HTN Caused by the actual pregnancy!
    - “Caused” by pregnancy – “cured” by delivery
      * BUT 20% cases of eclampsia occur > 48 hr post-partum
        + Can even develop this up to 2 days after delivery!!!
    - Definition of **Pre-eclampsia**:
      * Develops after 20th week of gestation
      * Elevated blood pressure >140/90 mmHg
      * Proteinuria > 300 mg/day
    - **Severe** pre-eclampsia can be life threatening
      * When BP >180/110 and this can be life threatening
    - Rarely, **seizures** develop – becomes “**eclampsia**”
  + **CHRONIC HYPERTENSION**
    - Most drugs used prior to pregnancy can be used
    - **ACEIs and ARBs, however, are contraindicated** – adverse effects on or death of fetus
    - Avoid too aggressive therapy and too low BP
      * May compromise uteroplacental blood flow
    - **METHYLDOPA** (*Aldomet*®, 1962)
      * Traditional **drug of choice** for therapy begun ***during*** pregnancy (pregnancy category B) and they haven’t been treated previously for HTN
        + Little effect on uteroplacental flow or fetal hemodynamics
        + Does not affect fetus or neonate
      * MECHANISM
        + Competes with DOPA in DA, NE, EPI synthesis pathway – produces Me-DA and Me-NE (methyl derivatives of agents) in brain

The presence of the methyl group makes it resistant to MAO metabolism

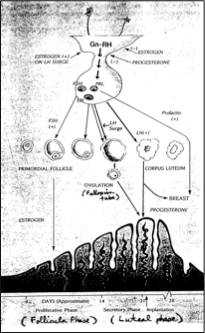
* + - * + **Me-NE** is an **a2 agonist** in the brain (like Clonidine), inhibits sympathetic output to vascular SM and heart

this is good because if you peripherally vasodilate the SNS will reflex stimulate the heart and if you inhibit the β1 receptors (like w/ β blockers) the SNS will reflex constrict the arterioles. If you inhibit the output of the SNS from the brain you inhibit both of those things at the same time and maintain the normal regulatory mechanisms for the baroreceptor reflex and you can still cause vasoconstriction (its not like using an α blocker) so you can still regulate your BP well

* + - * + **Me-NE** is also an **a1** **agonist** in vascular SM so does not block vasoconstriction or baroreflex completely
        + Similar result to clonidine, but less bradycardia
        + Renal blood flow and function not affected
      * SIDE EFFECTS: (brain α2) sedation, dry mouth, prolactin↑
        + Minimal side effects
  + **Other ANTIHYPERTENSIVE DRUGS used in PREGNANCY**
    - **LABETALOL**
    - Atenolol
    - Nifedipine-- Ca channel blocker
    - Thiazides
    - **HYDRALAZINE**
* ***SEVERE*** PRE-ECLAMPSIA (>180/110)
  + LIFE-THREATENING condition that requires treatment, if **immediate** delivery not chosen
    - Goals: 1) lower BP, and 2) prevent seizures
  + **HYDRALAZINE** (*Apresoline*®) **(IV or IM) and/or LABETALOL (IV) – lower BP**
    - Hydralazine and labetalol often used in combination
      * Hydralazine is a vasodilator that works on the arterial side of circulation and to tx moderate to severe HTN it is used with a β-blocker and a diuretic
    - For hypertension, when diastolic BP > 110 mmHg
  + **NIFEDIPINE** (Oral)
  + **SODIUM NITROPRUSSIDE** (IV)
  + **MAGNESIUM SULFATE – to tx seizures if they do develop**
    - ***Prevents*** seizures in severe pre-eclampsia and patients with CNS manifestations, (headache, visual problems)
      * Reduces risk of eclampsia by 58%, death by 45%
    - ***Treats*** seizures of eclampsia
      * We know from the GI lecture that if its give orally it stays in the gut and works as a laxative
    - ***Prophylaxis*** postpartum for women with CNS manifest.
    - ADMINISTRATION
      * Maintain plasma MgSO4 at 4-7 mM
        + 4 g IV over 20-30 min, then infusion of 1-3 g/hr
    - MONITORING
      * Monitor reflexes, respiration, Ca gluconate to reverse

**PHARMACOLOGY OF THE REPRODUCTIVE HORMONES**

**ENDOCRINE CONTROL OF OVULATION AND IMPLANTATION**

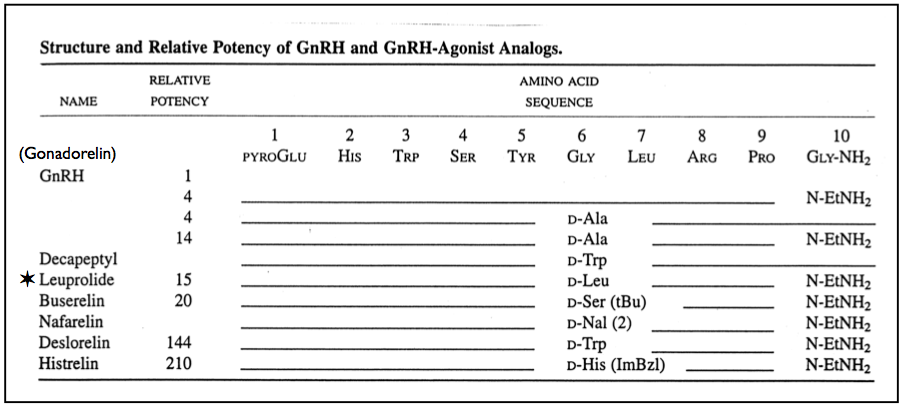


The Hypothalamus secretes a master hormone called GnRH (secreted in a pulsatile nature) which has actions on the pituitary gland and will stimulate the pituitary gland and gonadotropin proteins hormones are released. The first gonadotropin that is released is FSH and it travels to ovaries and stimulates the follicle and the main effect that FSH has is that is causes it to secrete estrogen (17 β estradiol is the most important estrogen in humans). Estradiol in the uterus is a trophic hormone and tends to cause proliferation of target tissues and it will stimulate the endometrial cells of the uterus to grow (must have growth of endometrial layer for implantation). Estrogen also has a positive effect on hypothalamus pituitary axis especially on GnRH secretion—causes another round of GnRH release. This second surge of GnRH causes the release of LH. LH goes to the follicle cell and stimulates it to ovulate and release eggs into the fallopian tube. LH also cause the follicle to differentiate into the structure called the corpus luteum. (CL). CL produces progesterone. Progesterone does 3 important things: 1. Goes to rapidly growing endometrial layer of the uterus and causes them to stop growing and differentiate into their secretory phase. This allows the endometrium to now be able to support a fertilized egg. 2. Progesterone along with prolactin goes to the breast and aids in milk production. 3. It also effects the hypothalamus-pituitary axis Both high levels of E and P have a negative effect on GnRH secretion. So if an egg does not implant into the uterus, the high levels of E and P ↓ GnRH and the LH stimulation of the CL ↓ and the CL atrophies and P ↓ and the endometrial layer can no longer be maintained and you have shedding of the endometrial layer and menstruation. However (not illustrated) if the egg is fertilized and implants there is problem—the uterus still need continuous P for early stages of egg and fetal development to proceed. But by this cycle the uterus cannot keep getting its P so the way we get around this is that the fetus takes matters into its own hands and the placental tissues which are derived from tissues in fertilized eggs. And these placental tissues secrete a gonadotropin that essentially has LH activity called hCG and it goes to the CL and doesn't allow it to atrophy so P is still released by the CL.

**GNRH AND GONADOTROPINS**

* **GONADOTROPIN-RELEASING HORMONE (GNRH)**
  + Decapeptide secreted by the hypothalamus
  + Serum half-life = 4 min (needs a rapid turn over rate to be able to work in a pulsatile fashion)
  + Secretion occurs in pulses
    - Pulsatile IV or subcutaneous administration @ 60 - 120 min ➙ FSH and LH secretion
      * Physiological pulsatile nature is essential for stimulating the pituitary but if the pituitary is exposed to continuous chronic GnRH then it actually has a inhibitory effect on pituitary
    - Continuous administration ➙ gonadotropin suppression
  + Synthetic analogs now available
    - Longer half-lives
    - Higher receptor-binding affinities –more potent drugs
    - Synthetic GnRH = **GONADORELIN**
* **STRUCTURE AND POTENCY OF GNRH AND ANALOGS**

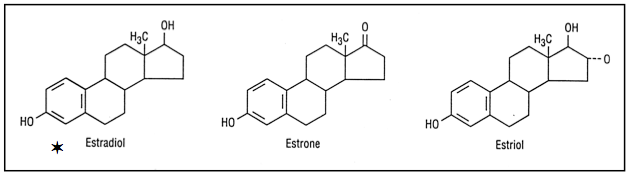
🡨Gly at position 6 is very important for binding at the GnRH receptor so substitutions at this point can allow for tighter binding of compounds🡪 leading to hyper potency. Substitution at Gly at position 10 give an ethylamide group which gives compounds longer half lives. **LEUPROLIDE** was one of the first synthetic high potency analog to be made.



* **GONADOTROPINS**
  + Historically have been known as **MENOTROPINS**
    - From urine of postmenopausal women they have higher levels of LH and FSH
      * FSH and LH are large protein hormones (α and β chain on each) and you can make these from scratch but they are difficult and expensive to make from scratch.
    - Contain naturally-modified FSH and LH activity of low potency
  + **UROFOLLITROPIN** ✶
    - Menotropin containing only FSH activity
    - Used more commonly than recombinant FSH because its cheaper to use.
  + **RECOMBINANT FSH (rFSH)**
    - Follitropin alpha and beta
      * Identical except for carbohydrate side-chains
      * Identical activities / more expensive
  + **HUMAN CHORIONIC GONADOTROPIN** (hCG) ✶
    - Isolated from urine of pregnant women
    - Secreted by placenta🡪 goes into the maternal blood stream🡪 gets secreted by the kidneys in the moms urine
    - LH activity (ovulation and progesterone secretion)
  + **RECOMBINANT hCG (rhCG)**
    - Choriogonadotropin alpha
    - Most expensive
* **THERAPEUTIC USES OF GNRH & ANALOGS**
  + Induction of ovulation in amenorrheic women (cant produce enough GnRH)
    - Gonadorelin 5 ug @ 90 min
      * Use this b/c you want it to have rapid turn over so you can release it in a pulsatile fashion to stimulate the pituitary
    - One cycle of treatment often enough to induce ovulation
  + In vitro fertilization—used when you have blocked fallopian tubes
    - Continuous **LEUPROLIDE** to suppress LH & FSH
      * High potency long acting GnRH
    - Use Controlled gonadotropin doses (**UROFOLLITROPIN** & **hCG**) 🡪 until you see follicle development and ovulation which mostly likely will lead to an egg in the fallopian tube
      * You can then retrieve the egg and fertilize it in the petri dish and implant it in the uterus
  + Delayed puberty - pulsatile (**GONADORELIN**)
  + Precocious purberty - continuous (**LEUPROLIDE**) to suppress the menses
  + Endometriosis (usually due to overstimulationg by estrogens)- **LEUPROLIDE** to inhibit the ovulatory cycle
  + Prostate cancer - **LEUPROLIDE**, HISTRELIN, GOSERELIN
    - Testosterone stimulates the growth of prostate tissue and in older men you can have BPH or prostate cancer and you use high potency analogs to inhibit testosterone secretion.

**ESTROGENS**

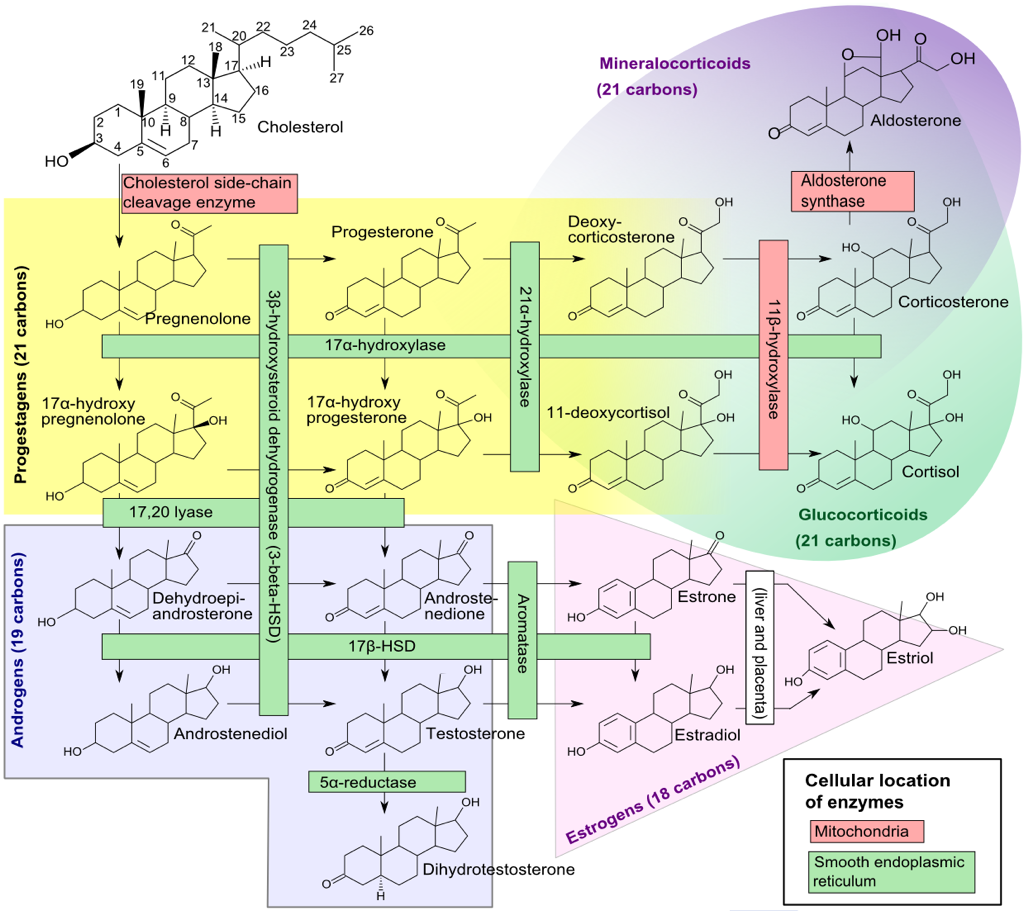
* **ESTROGEN PREPARATIONS**
  + **NATURAL ESTROGENS**



* + - * \*KNOW **ESTRADIOL—**secreted by the ovaries and adrenal glands. They all pretty equal in their potency at the receptor but estradiol is the one that is secreted at much higher concentrations by the ovaries. Dominant estrogen that is controlling the female reproductive cycle. Pharmacologically 17 β estradiol is hardly ever used.
    - Structurally similar compounds with similar potencies
    - Quickly inactivated by liver by conjugation (sulfation and glucoronation). Rapid elimination by kidneys
    - Not orally effective. Administration ➙ transdermal or intramuscular
  + **CONJUGATED ESTROGENS** ✶
    - Obtained from pregnant mare’s urine or stallion
    - Circa 60% **SULFATED ESTRONE**—even thought they’ve been sulfated they still bind to the estrogen receptor and still work but you have to use them at higher doses. Nice thing about these is they have already passed metabolism by the liver (where they were sulfated) making them orally effective.
    - Orally effective at high concentrations
    - Common drug: **PREMARIN**® (Wyeth)
    - **PREMARIN + PROGESTIN = PREMPRO**® (Wyeth)
      * Used to be the most commonly prescribed estrogen
  + **SYNTHETIC, STEROIDAL ESTROGENS (MOST IMPORTANT CLASS)** 
    - **ETHINYL ESTRADIOL**✶**, QUINESTROL**, **MESTRANOL**
      * Dominant synthetic estrogen in oral contraceptive pills
    - Potent agonists at the estrogen receptor
    - Less-rapidly metabolized by liver 🡪 Longer duration of action
    - Orally effective
  + **SYNTHETIC, NON-STEROIDAL ESTROGENS**
    - **DIETHYLSTILBESTROL (DES)**
      * Moderately potent agonist, slowly inactivated by liver, orally effective, common in past usage
      * The structure of this compound doesn't look like it’d be an agonist at the E receptor but the two ethers actually form a benzene ring in space and the structure begins to look like a steroid
    - **CHLOROTRIANISENE**
      * Very fat soluble, stored in adipose tissue and slowly released
* **THERAPEUTIC USES OF ESTROGENS**
  + Dysmenorrhea
    - Difficult or painful menstruation
    - **Contractions** caused by **overstimulation of uterus by prostaglandins—**this is occurring is response to the ovulatory cycle. So rx an OC pill and you can inhibit the ovulatory cycle (progestins in OC pills also inhibit the secretion of prostaglandins too)
    - Usual therapy: NSAIDs
    - For intractable dysmenorrhea: Inhibit ovulatory cycle by chronic administration of estrogens and progestins
  + Hirsutism
    - Masculinization due to excess androgen production by ovary or adrenals
    - Deeping of voice, facial hair, etc
    - Estrogens can combat the over production of androgens
  + Contraception
  + Menopause
    - Most of symptoms of menopause are caused by cessation of ovulatory cycle and estrogen withdrawal
    - Symptoms attributable to lack of estrogen stimulation
      * Hot flashes, sweating, atrophic vaginitis
    - Estrogen replacement therapy (ERT), usually in conjunction with  progestin
      * First they just gave ethinyl estradiol but they found that it was associated with ↑ risk of endometrial cancer so the progestins were added to protect against this.
  + Postmenopausal Osteoporosis
    - Dramatic loss of bone matrix due to estrogen deficiency it can lead to fractures, etc
      * Estrogen is trophic at bone tissue—it promotes growth so loss of it will lead to bone matrix loss
    - Greatest bone loss occurs within five years of menopause and then declines gradually after that
    - Therapy: chronic or cyclic administration of estrogen + progestin (same reason that progestin was added to tx menopause) immediately after menopause or at onset of bone loss (it was previous prescribed for life after this but that has changed and will be discussed later). Withdrawal of therapy may result in accelerated bone loss
  + Conventional “Wisdom” 🡪 ERT for life.
    - ★ New risk evidence has undermined this practice ★
* **NON-STEROIDAL DRUGS FOR OSTEOPOROSIS** 
  + **BISPHOSPHONATES**
    - MOA:
      * Retard dissolution of hydroxyapatite crystals
      * These compounds go into bone and replace the pyrophosphate with this structure and it becomes part of the bone crystal structure. Considered permanent components of bone structure one they are administered. The reason they prevent bone loss is b/c these compounds stabilize the bone mineral, they are less likely to be cleaved, etc leading to much slower turn over rate of bone mineral
    - Examples
      * Pyrophosphate
        + Pyrophosphate crystals are an important component of bone mineral
      * **ALENDRONATE** ✶ (Fosomax®)
      * **ETIDRONATE** (Didronel®)
      * **PAMIDRONATE** (Aredia®)—3rd generation drug w/ the best efficacy
    - Pharmacodynamics:
      * 1-10% oral dose is absorbed –so 90% is wasted
      * Of that 10% that gets absorbed 50% accumulates in bone and 50% excreted in urine so really doesn't do much of anything to other parts of the body which is good—specific for targeting bone tissue
    - Used in Paget’s disease (degenerative loss of bone due to a genetic mutation) as well as post menopausal osteoporosis
    - Recently approved for treating hypercalcemia that arises from certain kind of Malignancies/cancer
    - **ALENDRONATE**:
      * Now commonly used for post-menopausal osteoporosis
      * Also shown useful in preventing male vertebral fractures (so women and men can benefit from this drug)

**ANTI-ESTROGENS**

* Antagonize Action of Estrogen at the Receptor
  + ✶**TAMOXIFEN**
  + Clomiphene
  + Historically thought to be global competitive antagonists at the E receptor— which bind but do not activate the estrogen receptor blocking estradiol mediated responses
    - but as its been studied this view is changing because competitive antagonist should have a global action (block all estrogen mediated responses) and shouldn't have agonist activity anywhere.
  + Now better viewed as **SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)**
  + **CLOMIPHENE** (Clomid®)
    - Used in the treatment of anovulatory infertility
    - Acts by inhibiting estrogen-mediated repression of GnRH release by hypothalamus
      * If you have too much estrogen being produced by the adrenals and ovaries you will suppress the hypothalamus-pituitary axis (just like having an endogenous OC pill) so you wont ovulate.
      * Antagonist at the hypothalamus but doesn't work as an antagonist at the breast like tamoxifen.
    - Not effective in patients with pituitary or ovarian dysfunction
    - Dosing regimen causes rise in plasma LH and FSH levels by 5th day
      * Single dosing regimen results in single ovulation
      * Repeated dosing required for subsequent ovulations
    - Normal ovulatory cycle not usually resumed
    - Effectiveness
      * 80% of patients ovulate
        + of the 80% 40 to 50% of these become pregnant
  + ✶ **TAMOXIFEN** (Nolvadex®)
    - Orally effective
    - Used to treat **steroid-dependent breast cancer**
      * 2 types of breast cancers
        + **Estrogen receptor positive**—these are not the best kind b/c they grow slower (still can be dangerous though) and they are stimulated to grow by estrogens so you can slow down the growth by txing with an E receptor antagonist.
        + **Estrogen receptor negative**—these are the worst kind b/c they are faster growing and more likely to mets and kill you
    - Inhibits estrogen stimulation of cancer growth
    - Can be used on pre- and post-menopausal women with ER- positive tumors
    - Shown to be just as effective as cytotoxic anti-neoplastics  (chemotherapy)
      * Many fewer serious or unpleasant side effects
      * Becoming drug of choice
    - Side effects:
      * Hypercalcemia—b/c you antagonizing E receptors at the bone
      * Bone pain-- b/c you antagonizing E receptors at the bone
      * Increased risk of endometrial cancer—this is an agonist effect which is weird b/c we call this drug an antagonist. It is acting like an estrogen in the uterus
* **ANTI-ESTROGENS (SERMS)**
  + **RALOXIFENE** (Evista®)
    - Approved as **agonist for postmenopausal osteoporosis**—stimulates bone density
    - **Antagonist at uterus**
    - Early evidence of **antagonism at breast**
    - Some physicians are starting to use this as HRT in postmenopausal women
* **ANTI-ESTROGENS (INHIBITORS OF BIOSYNTHESIS)**
  + Used to treat **E Receptor positive Breast Cancer Resistant to Tamoxifen**
    - Want to make sure there is no estradiol present (synthesized in the ovaries, adrenal glands, and to a lesser extent the liver) to stimulate the growth of these cancers because blocking the receptor no longer works



* + **AMINOGLUTETHIMIDE** (Cytadren®)
    - Blocks conversion of cholesterol to pregnenolone in adrenals and other tissues (blocks the first step in the synthesis of all steroids)
    - Given at high concentrations this drug can blocks aromatase which converts androstenedione and testosterone to estradiol—but b/c it blocks all steroid synthesis you would not use this very commonly
    - Reduces all steroid synthesis, including estradiol
      * So also will need replacement therapy especially for glucocorticoids🡪 Hydrocortisone replacement required
* **ANTI-ESTROGENS (INHIBITORS OF BIOSYNTHESIS) AROMATASE INHIBITORS**
  + ✶ **ANASTROZOLE** (Arimidex®) and **LETROZOLE** (Femara®)
    - Anastrozole is the most commonly prescribed
    - Binds reversibly and is a **competitive non-steroidal inhibitors** of aromatase responsible for conversion of androgens to estrogens
      * Aromatase is responsible for conversion of androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) so if you block this enzyme this conversion does not take place so you don't make estrogens.
  + **EXEMESTANE** (Aromasin®)—2nd generation
    - Non-reversible steroidal inhibitor of aromatase—so much longer duration of action in inhibiting the enzyme

**PROGESTINS**

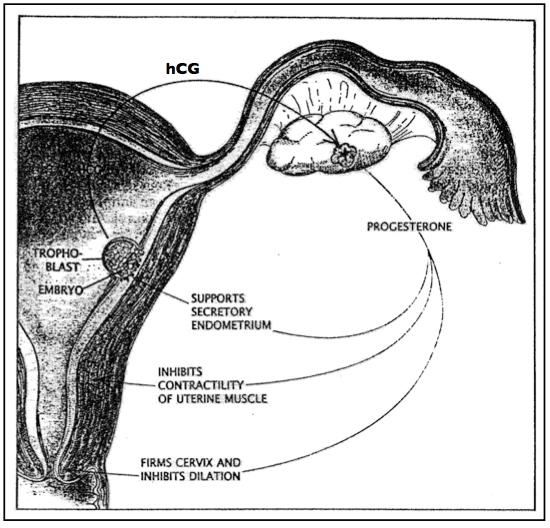
* **TWO CLASSES OF SYNTHETIC PROGESTINS ARE AVAILABLE**
  + **DERIVATIVES OF PROGESTERONE (derived from native progesterone)**
    - 21 carbon steroids
      * These are true progestational agents🡪 Can stimulate endometrial secretions and support pregnancy in test animals
      * Variable androgenic and estrogenic side effects (draw back of these drugs)
    - Examples:
      * **MEDROXYPROGESTERONE ACETATE (Provera®)—most commonly Rx**
      * **HYDROXYPROGESTERONE CAPROATE**
      * **MEGESTROL ACETATE**
  + **DERIVATIVES OF NORTESTOSTERONE (androgen compound)**
    - 19 carbon steroids
      * Can stimulate cellular changes in endometrium but CANNOT support pregnancy in test animals b/c these agents do not cause differentiation of the endometrium into the secretory state which is needed for implantation (so not true progestational agents)
      * Advantages
        + More effective inhibitors of gonadotropin secretion (so inhibits ovulatory cycle by inhibiting HP axis). Majority of oral contraceptives now employ a nortestosterone derivative
        + Late generation analogs have reduced androgenic and estrogenic side effects
    - Examples:
      * ✶**NORETHINDRONE** (Norlutin®)
      * **L-NORGESTREL—now a days this is becoming more popular**
      * **NORGESTIMATE**

**ANTI-PROGESTINS**

* ✶ **RU486** (**MIFEPRISTONE**)
  + Controversial abortifacient (used to induce abortions)
  + Binds both progesterone and glucocorticoid receptors - preventing gene transcription
    - Also very good antagonist at glucocorticoid receptor but its typical used to block progesterone receptor
  + Other potential therapeutic uses:
    - Inhibition of progesterone- and glucocorticoid-dependent tumors
    - Effective in treatment of fibroid tumors
    - Cushing’s disease
    - Post-coital birth control—better ways of achieving this now

**CONTRACEPTION**

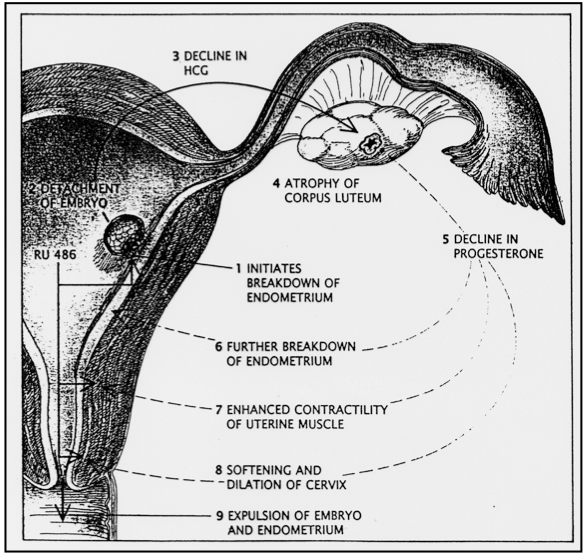
* **CONTROL OF IMPLANTATION BY PROGESTERONE AND HCG**



RU486 causes breakdown of the endometrial layer because the progesterone cannot be stimulated to maintain it and once that endometrial layer starts to break down you get partial detachment of the embryo and viability of the embryonic cells starts to ↓ and its ability to produce hCG also ↓ which leads to ↓ maintenance of the CL (which is producing endogenous progesterone) so this also acts to ↓ progesterone. With ↓ P you also get ↑ breakdown of endometrial layer and enhanced uterine contractility b/c now PG can be secreted and these contraction combined w/ the partial detachment due to atrophy of the endometrium leads to complete detachment and expulsion of the embryo. You also get a softening and dilation of the cervix Most serious side effect of this treatment is BLEEDING which can be sufficient enough to cause death.

Early stages of implantation and development. Trophoblasts cells that go on to form the placenta are growing very rapidly and producing hCG to signal to the CL to continue to making progesterone so the endometrial layer is maintained for development. Progesterone supports the secretory endometrium, it also inhibits the contractility of the uterine muscle by inhibiting the production and secretion of PG’s, and it firms the cervix and inhibits the dilation of it.

* **ABORTIFACIENT ACTIONS OF RU486**



* + - RU486 alone: 400-600 mg/day (oral) for 4 days = 85% effective –no longer used these days
    - RU486 (600 mg) + Prostaglandin E1 (to ↑ contractions) = 95% effective 🡨preferred use of this
* **DIVERSE THERAPEUTIC APPROACHES TO CONTRACEPTION**
  + **COMBINED ORAL CONTRACEPTIVES (COCS)**
  + **TRANSDERMAL CONTRACEPTION (THE “PATCH”)—**estrogens on patch that get slowly absorbed
  + **INTRADERMAL CONTRACEPTION (NORPLANT®) --**capsule inserted under the skin giving very long acting effects
  + **POST-COITAL BIRTH CONTROL (“MORNING AFTER PILL”, OR PLAN B®)**
  + **CONTRACEPTIVE RINGS (NUVARING®)—**estrogen (and progestin) in a ring that is inserted by the uterus
    - There is also P-only vaginal rings
  + **INJECTABLE (DEPO-PROVERA®)**
* **TRANSDERMAL CONTRACEPTION**
  + **ORTHO EVRA**® – The “Patch”
  + Transdermal administration of **NORELGESTROMIN** AND **ETHINYL ESTRADIOL**
  + Norelgestromin = active metabolite of norgestimate (so cant use this in the patch b/c to be active it must be converted to norelgestromin in the liver)
  + Patch applied weekly
  + Advantages:
    - Bypasses hepatic metabolism
    - Lower peak plasma concentrations of drug than COCs
    - Presumed lower rates of side effects
    - Better compliance
    - Comparable failure rates to COCs in typical usage
  + Disadvantages:
    - Skin allergies --but can rotate patch placement to get around this
    - Higher steady state concentrations of drug than COCs
* **INTRADERMAL CONTRACEPTION**
  + **NORPLANT II**® (Jadelle®)
  + Two flexible capsules containing **NORGESTREL (3rd generation progestin)**
  + Inserted under skin on upper arm or thigh
  + Insertion and removal require minor surgery with local anesthetic
  + Effective for up to 5 years
  + Approved in 1990 in USA
  + Many millions of users worldwide
  + Serum steroid levels are 1/5 to 1/3 of oral contraceptives
  + Fewer side effects
  + Effectiveness:
    - After One Year: 0.2 failures per 100 women years
    - After Five Years: 0.8 failures per 100 women years—same as COC
* **POST-COITAL BIRTH CONTROL**
  + High doses of estrogens historically taken at high doses for 5-6 days following intercourse
  + Effective when begun by 72 hours post-coitum
  + Estrogens typically used: **CONJUGATED ESTROGENS**, **ETHINYL**  **ESTRADIOL**
  + New studies suggest that 3rd generation progestins are more effective**.**
  + **“Plan B” drug** (**L-NORGESTREL**) approved by FDA in 1999; as over-the-counter drug to adults in 2009.
    - Effectiveness: 89% (72 hours), 95% (24 hours)
  + Mechanism – Delays ovulation and sperm migration, found not to disrupt implantation
    - Remember these are not true progestational agents—they don't support the secretory phase of the endometrium so now the sperm have a hard time migrating up the uterus and fallopian tubes to get to the egg
    - In women who have ovulated Plan B has no protective effect b/c it doesn't block implantation or fertilization of egg
  + Strong side effects –these are minimized w/ Plan B though
    - Nausea
    - Vomiting
    - Severe cramps
* **COMBINED ORAL CONTRACEPTIVES (COCS)**
  + Monophasic
    - Constant dose of estrogen + progestin over 21 days
  + Diphasic and triphasic—these were developed to deal with the problem of irregular spotting associated with the monophasic approach
    - Constant low dose of estrogen + variable dose of progestin
    - **Diphasic**: progestin dose increased once at approx. day 10, higher dose maintained to day 21.
      * Somewhere in the middle you ↑ the dose of progestin
    - Most common is **Triphasic** - Progestin increased in 2nd and 3rd week of 21 day dosing regimen
      * Progestin is ↑ twice (at end of 1st week and end of 2nd week)
  + Progestin-Only (“Mini-Pill”)
    - Low dose of progestin
    - Taken every day—fairly effective
  + Most commonly used drugs:
    - ✶Estrogen**: ETHINYL ESTRADIOL** (Estinyl®)
    - ✶ Progestin: **NORETHINDRONE** (Norlutin®), **L-NORGESTREL** (Ovrette®)
* **FAILURE RATES OF ORAL CONTRACEPTIVES**
  + Monophasic: 0.7 per 100 women years
  + Phasic: 1.0 per 100 women years
  + Progestin Only: 3.0 per 100 women years
  + Combination and phasic types are the safest
  + Why use “mini-pill”? B/c there are a lot of side effects associated with estrogen therapies of all sorts.
    - If you have patient w/ a history of one of the side effects from the estrogens (like migraines) maybe you’ll try the mini pill instead
* **ADVERSE SIDE EFFECTS OF COC**
  + **GENERAL CONSIDERATIONS**
    - Incidence of serious side effects is low
      * You have 3-4x’s greater risk of dying from this drug than those who don't take the drug
    - Many reversible changes to intermediary metabolism occur but long-term consequences not well understood
    - Minor side effects are frequent but transient (tend to occur w/in the first month or two of usage and then your body acclimates)
    - 33% of COC users stop therapy for reasons other than planned pregnancy
      * Is it because
        + Do minor side effects add up?
        + Is dosing regimen too cumbersome?
        + Are serious side effects too scary for them?
      * We don't know.
  + **MILD SIDE EFFECTS**

|  |  |
| --- | --- |
| **COMPLAINT** | **SOLUTION** |
| Nausea  Breast discomfort  Fluid retention | Decrease estrogen (b/c usually do to overstimulation by estrogen component) |
| Weight gain  Depression  Hair growth | Decrease progestin (b/c these things are usually caused by the progestin) or switch to 3rd generation drug (e.g. **NORGESTREL**) |

* + - Headache
      * Common but transient (first couple months of usage)
      * For recurrent migraines - stop therapy due to risk of stroke
    - Amenorrhea
      * Short to prolonged period of non-ovulation after cessation of treatment
  + **SERIOUS SIDE EFFECTS—**remember the relative risk for these things is pretty low
    - **Thrombotic Disorders**
      * Thromboembolism and thrombophlebitis (first serious side effect discovered)
      * Pulmonary embolism
      * Thrombotic and hemorrhagic strokes
      * Risk of thromboembolism:
        + Non-users - 1 per 1000 women years
        + Users - 3 per 1000 women years
        + Risk rises within first month; remains constant –no cumulative risk
        + Risk returns to normal within one month of discontinuance
      * Underlying physiological cause:
        + Decrease in Anti-thrombin III (major inhibitor of blot clotting so more likely to clot)
    - **Cardiovascular Disorders**
      * Myocardial Infarction (heart attack)
        + Risk of MI increased slightly for all COC users (like 2-3 fold ↑)
        + Risk much greater in women with predisposing conditions

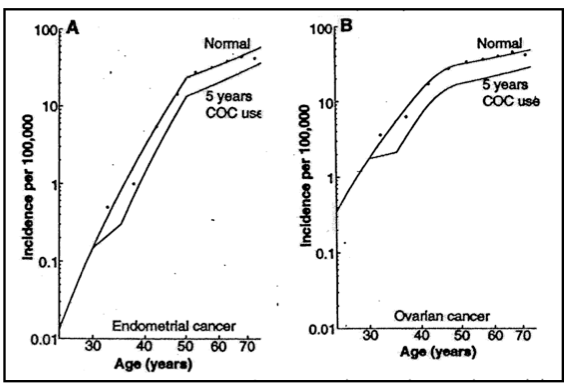
Diabetes or smokers

* + - * + Underlying physiological cause:

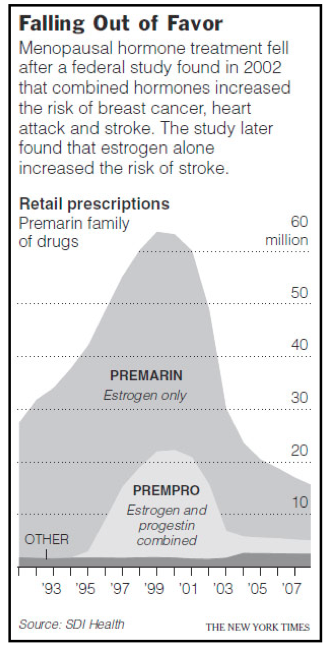
Decreased levels of HDL and increased levels of LDL cholesterols

* + - * Hypertension
        + 3-6 fold increase in the incidence of overt hypertension
        + Contributing factor to increased thrombolic and coronary risk
    - **Cancer Complicated and Controversial**
      * Liver Cell Adenoma—benign growths on the liver
        + Prolonged use (>3 years) leads to increase risk of benign hepatic adenomas

Chronic users are at a higher risk

* + - * + Usually not life-threatening - unless adenoma ruptures
      * Cervical and Vaginal Cancer
        + Clear risk due to use of diethylstilbestrol (DES)
        + Risk only for daughters of women who used DES during 1st trimester of pregnancy—this is a historical problem—doctors prescribed it for women who wanted to get pregnant which is not what it does!
      * Breast Cancer
        + Controversial. Most studies show increased risk.
    - **Endometrial and Ovarian Cancers**
      * Several studies show 2-15X risk of endometrial cancer for estrogen-alone therapies
      * Clear evidence that risks of endometrial and ovarian cancers decrease in women taking COCs
      * COCs resulted in 2-fold **protection** against endometrial (12 vs 23 per 100,000) and ovarian cancer (18 vs 30 per 100,000)
      * Magnitude of protection constant with age (35+ years)
      * “Hormonal Chemoprevention of Cancer in Women” Henderson et al, Science 259: 633 (1993)
      * 
        + showed that it is the Progestin that is protective against these cancers b/c remember P stimulates rapidly growing endometrial cells to stop rapidly growing and differentiating cause the endometrium to go into the secretory phase. P blocks E growth properties on the endometrium.

**SIDE EFFECTS OF ESTROGEN REPLACEMENT THERAPY (ERT)**

* Conventional Wisdom
  + ERT alleviated symptoms of menopause
  + ERT protected against bone loss
  + ERT in combination with progestin protected against endometrial and ovarian cancers
  + \*\*ERT protective against heart disease\*\*--THIS IS NOT TRUE
    - Early studies really were poorly done
  + Therefore, ERT for life encouraged in women over 50.
* Recent results of the NIH Women’s Health Initiative study:
  + 16,000 healthy women 50 to 79 years old
  + Estrogen plus progestin (Prempro® - Wyeth) compared to placebo group
  + Small decrease in bone fractures
  + Small decrease in colorectal cancer—not sure why
  + 26% increase in breast cancer
  + 29% increase in heart attacks
  + 41% increase in strokes
  + 22% overall increase in cardiovascular disease—opposite of what used to be thought
* Bottom Line? ERT only for moderate to severe symptoms of menopause (hot flashes and night sweats) and as second-line drug for prevention of osteoporosis (when bisphosphonates don't work)
* Side Effects of the WHI Study
  + “What happened is that medical practice, as it often does, got ahead of medical science. We made observations and developed hypotheses – and forgot to prove them.” Susan M. Love, NY Times, July 16, 2002

**ANDROGENIC STEROIDS**

* Produced in testis, ovary and adrenals
* Testosterone
  + Produced in Leydig cells of testis
  + Converted to Dihydroxytestosterone (DHT) by Sertoli cells and other target tissues
  + DHT is more potent agonist
* Physiological processes stimulated
  + Androgenic effects
    - Development of male sex organs
    - Spermatogenesis
    - Larynx enlargement
    - Hair growth
  + Anabolic Effects
    - Bone growth
    - Muscle development
    - Erythropoiesis

**ANDROGEN DRUGS**

* **TESTOSTERONE**
  + Clinically ineffective
* **ESTERIFIED** **TESTOSTERONES**
  + Examples: **TESTOSTERONE** **CYPIONATE**, **TESTOSTERONE** **PROPIONATE**
    - Have longer duration of action (2-3 weeks)
    - I.M. via oil suspension
* **SYNTHETIC** **TESTOSTERONES**
  + Examples: **METHYLTESTOSTERONE**, **FLUOXYMESTERONE**
  + Orally effective
* **FINASTERIDE ✶**
  + Blocks the enzyme that converts testosterone to DHT in target cells
  + Subject of curious pricing
    - **PROSCAR**® - Benign prostatic hyperplasia - 5 mg/day = $0.47/mg –CHEAPER
    - **PROPECIA**® - Male-pattern baldness - 1 mg/day = $1.67/mg

**ANABOLIC STEROIDS**

* Can develop compounds that are more anabolic than androgenic (reflected in the ratios of the table bleow)
* Anabolic effects include
  + Trophic effects on muscle, bone and blood cells
  + Reduction in nitrogen excretion
* Testing in animals has uncovered steroids in which androgenic and anabolic effects can be separated

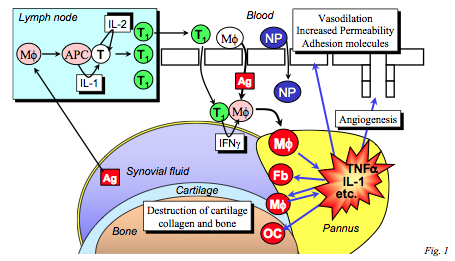
|  |  |
| --- | --- |
| **DRUG** | **ANDROGENIC : ANABOLIC ACTIVITY** |
| **TESTOSTERONE** | 1:1 |
| **FLUOXYMESTERONE** | 1:2 |
| **ETHYLESTRENOL** | 1:8 |
| **OXANDROLONE** | 1:13 |

* Separation of anabolic and androgenic effects not as effective in humans
* In female athletes
  + Marked increase in muscle mass, strength and aggressiveness (highly anabolic in women)
  + Acute “masculinization” - hirsutism, deep voice, depressed menses
* In male athletes: questionable efficacy? The level of training these athletes undergo probably has more to do with the ↑ in muscle mass they see than the anabolic steroids themselves
* In both sexes: danger of liver disease (jaundice) etc.

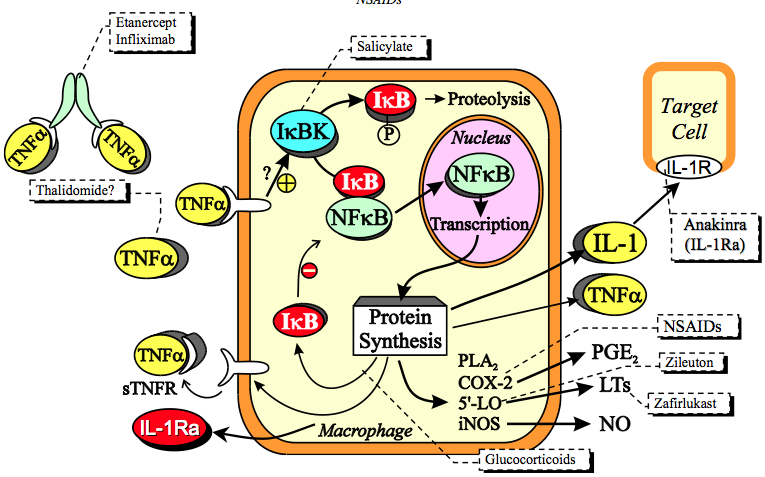
**MALE CONTRACEPTION?**

* + Many early studies “failed” to find effective male contraceptive
    - Due in part to over-emphasis on azoospermia
    - Notion was only takes one sperm to fertilize an egg and the male produces millions and millions of sperm the only way to achieve effective contraception in men is to get them down to producing NO SPERM but that's not necessarily true
  + New studies suggest that critical threshold is 3 X 106 sperm per ejaculation—below that is considered infertile
    - WHO Study
      * Testosterone injections
      * 98.6% effective
    - Anzac Research Institute (Australia) Study
      * Progestin (**NORGESTREL**) injection @ 3 months + testosterone implants or patches
        + B/c testosterone production is controlled by the same HP axis as women
        + 100% effective in small trial

**NSAIDS AND OTHER ANTI-INFLAMMATORY DRUGS**

**SIMPLIFIED MODEL OF RHEUMATOID ARTHRITIS**

* Bone is covered in cartilage to ↓ wear and tear on the bone and to ↓ the wear and tear on the cartilage the joint itself is encased in synovial membrane which secretes synovial fluid which acts like an oil to ↓ wear and tear on cartilage.
* RA is an autoimmune disease in which antibodies against self-proteins are generated
* Macrophages (M) engulf antigens that pass to lymph nodes and present peptides to T-cells leading to T-cell activation and proliferation. Requires interleukin-1 (IL-1) produced by macrophage and induction of IL-2 production by T-cells—IL-2 is important for T cell proliferation
* Activated, type 1 helper TH1-cells pass through blood to inflamed tissue, where they activate M that present the appropriate antigen - a process involving release of IFN γ
* Activated M release TNFα and IL-1, cause expression of adhesions proteins which attract other cells to the site which activate other M, fibroblasts and osteoclasts, and growth factors that promote angiogenesis (supply growing pannus)
  + Fibroblasts and osteoclasts especially start to secrete collagenases which start to break down cartilage and osteoclasts break down bone
* Prostaglandins, leukotrienes and NO released by M lead to vasodilation, and increased vascular permeability
* TNFα promote entry of WBCs from blood, e.g. by inducing expression of VCAM-1. “Pannus” –is swelling of synovial membrane thickened by infiltration of T cells, macrophages, fibroblasts- develops at junction of synovial membrane and cartilage
* Matrix metalloproteinases (MMPs) released from activated macrophages and fibroblasts break down cartilage
* Activated osteoclasts promote breakdown of bone
* **Net result joint damage and deformation**



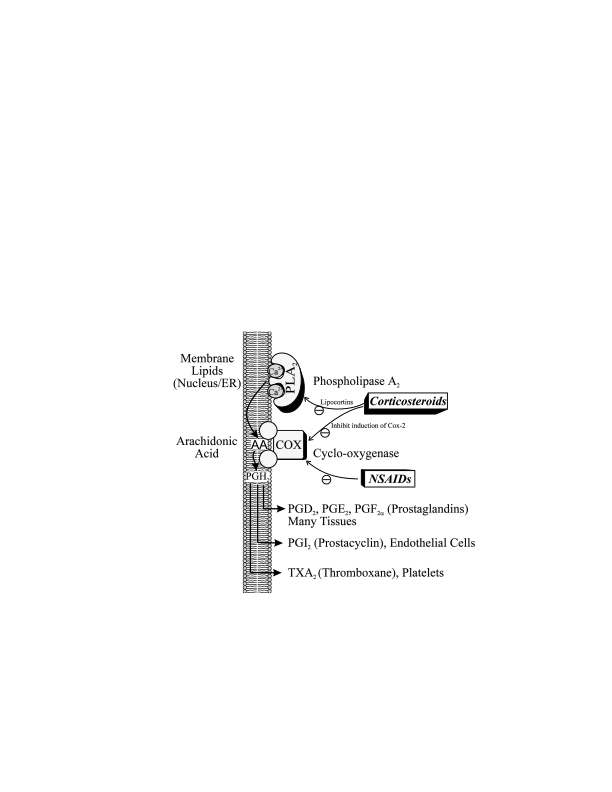
***Sites of Action of Anti-inflammatory Drugs****. TNF* *binds to its receptor and activates a kinase (I**BK) which phosphorylates the inhibitory protein I**B, which is then degraded. NF**B is then free to enter the nucleus and activate expression of various genes.*

-Zileuton was an important drug for asthma and now RA because it inhibits 5’-LO which makes LT’s. Zafirlukast is an antagonist of LT so it also is important in asthma and allergies but not indicated for RA. Most important anti-inflamm drugs are glucocorticoids (stim production of IkB as well as other things)

* + **TNF** plays a key role in propagating inflammation. TNF is a protein produced by macrophages following stimulation by various agents, e.g. lipopolysaccharide (LPS, or endotoxin) produced by gram-negative bacteria. TNF binds to specific receptors on a variety of cell types and activates a transcription factor called ***nuclear factor*** ***B*** (NF-B), which enters the nucleus and switches on the synthesis of many proinflammatory proteins.
    - These include:
      * Cyclooxygenase 2 (Cox-2))
      * 5’-Lipoxygenase (5’LO) and its activator protein-FLAP
      * Inducible nitric oxide synthetase (iNOS)
      * Phospholipase A2
      * Adhesion molecules in leukocytes and endothelial cells, which promote binding of leukocytes at the site of inflammation
      * TNF and interleukin-1 (IL-1) to amplify and propagate the process
  + Activation of NF-B occurs when its inhibitor, a protein called I-B, is phosphorylated by a specific protein kinase (I-B kinase, IKK) and degraded. The net effect is an increased synthesis of prostaglandins and leukotrienes
    - TNFα binds to its receptors and will activate a kinase which will phosphorylate IkB which inactivates it and released NFkB to go into the nucleus and turn on synthesis of proteins which drive inflammation—this causes more cytokines to be released and these inflammatory processes will result in the synthesis of PLA2 which releases arachadonic acid causing the synthesis of COX2 that generates the prostaglandins. Also induces the synthesis of 5’-Lipoxygenase which leads to leukotriene production. Inducible NOS gets activated and you get NO. To keep the inflammatory processes in control we have other actions like these cells produce IL-1 receptor antagonists so that will moderate effects on IL-1. Also produce other receptors for TNFα, which gets cleaved from the membrane making them soluble receptors and these are receptors obviously for TNFα and if its bound to a soluble receptor it is not activating the cell so this will ↓ TNFα effects. Most importantly It induced IkB inhibitory protein which will block NFkB effects in the nucleus.

**NSAIDS: MECHANISM OF ACTION**

* Aspirin is a derivative of a naturally occurring substance **salicylic acid,** which can be extracted from the bark of willow trees, and has been used for its medicinal properties for centuries if not millennia. Surprisingly, the role of salicylate in plants as a hormone involved in heat production and disease resistance has only been established in the past few years.
* Both aspirin and acetaminophen are synthetic products that have been in use for approximately 100 years; however, the relationship between NSAIDs and prostaglandins was not established until 1971.
* Most properties of aspirin are shared by other non-steroidal anti-inflammatory drugs (NSAIDs) and, therefore, we will focus on the pharmacology of aspirin. However, the **major** differences between aspirin, acetaminophen and other NSAIDs are very important.
* Most of the effects of NSAIDs result from their ability to inhibit the synthesis of **prostaglandins BY BLOCKING CYCLOOXYGENASE (COX)** and therefore, knowledge of their actions allows one to understand the therapeutic effects, the side effects and the limitations in the use of NSAIDs.
  + **COX-1**
    - Found **constitutively** in most tissues bound to ER
    - ***Important sites:*** GI tract, platelets and renal medulla
  + **COX-2** (1991)
    - **Induced** by cytokines (IL-1, TNFα--cytokines produced by endothelial cells, fibroblasts and macrophages during inflammation), LPS (lipopolysaccharides) in 2-6 hr in endothelial cells, fibroblasts and monocytes.
    - Membrane attached, ER and nucleus
    - Involved in inflammation (pain) and fever.
    - Found **constitutively** in the ***brain*** and the ***kidney*** (***macula densa***and***TAL of the Loop of Henle)***



Almost all tissues have the ability to synthesize prostaglandins. Prostaglandins are autacoids; i.e. they are synthesized have their site of action and are usually metabolized in the same tissue.

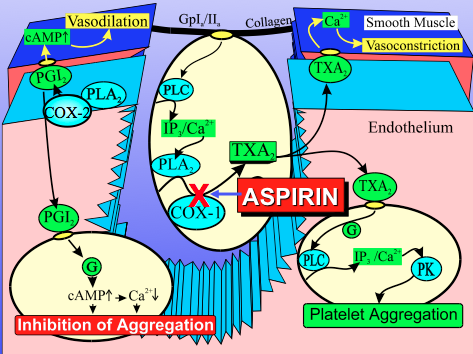
* **Step 1**
  + **Arachidonic acid** is a 20 carbon polyunsaturated fatty acid released from membrane phospholipids by **phospholipase A2**. (PLA2 in Fig. 1). This step is blocked by the action of **corticosteroids**.
* **Step 2**
  + Arachidonic acid is converted to PGH2 by **cyclooxygenase**. This step is blocked by **NSAIDS**. Two isoforms exist, **COX-1** and **COX-2,** both are membrane proteins. COX-2 synthesis is induced during inflammation and this induction is blocked by corticosteroids. The sensitivity of COX-1 and COX-2 may differ for any given drug.
* **Step 3**
  + PGH2 is converted to prostaglandins D2, E2, F2 or prostacyclin (PGI2) or thromboxane (TXA2) depending on the tissue. The effect of each also can vary from tissue to tissue depending on the receptors present and the process regulated by the receptor.

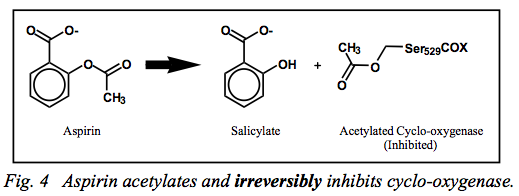
**THERAPEUTIC USES of NSAIDS**

* In the sections below, the uses of NSAIDs are reviewed. As you study this material, think about the validity of the following statement: NSAIDs have remarkably few effects in a healthy individual, because prostaglandins are only produced when an organ is stressed, e.g. when there is inflammation.
* ***TREATMENT OF PAIN - ANALGESIA***
  + **PGE2 and PGI2** sensitize nerves to **pain** stimuli - “Hyperalgesia”
    - These PG’s act on nociceptors that sense pain and lowering the threshold so less of the stimulus is needed to feel the pain so NSAID block these therefore you don't get this lowered threshold
    - **Ex:** histamine and bradykinin
  + **NSAIDs** block this by inhibiting prostaglandin synthesis in the affected tissue.
    - Useful for mild/moderate pain associated with headache, muscle ache, nerve ache, arthritis, dysmenorrhea.
    - Not useful for pain induced by exogenous prostaglandins. WHY? Because it blocks the production of the endogenous PG’s; once there are PG’s NSAIDS have no effect on them.
    - Comparison with opioid analgesics
      * 
        + NSAIDS act at the site of pain not on the CNS, like opioids
        + **Unlike opioids**, no tolerance or dependence develops to NSAIDs.
        + **Unlike opioids,** NSAIDs have a ceiling effect—only block the hyperalgesia to bring it back to normal.

Does it hurt less if you take an aspirin before hitting your thumb with a hammer? NO it just bring pain threshold to normal

* + - * + Opioids act in the CNS—they can ↓ respiratory function which limits their use
  + ***IMPORTANT: Difference in the mechanism of action of opioids and NSAIDs permits them to be used together. This allows lower doses of opioids to be used, delaying the development of tolerance and dependence.***
    - ***Ex: Vicoden ® (acetaminophen + hydrocodone)***
* ***TREATMENT OF FEVER - ANTIPYRESIS***
  + Fever is associated with infection and also with inflammation.
  + Most important agents responsible for fever are LPS, TNF and Interleukin-1 which are generated by infection and inflammation. When these are present in the blood stream, they interact with receptors on endothelial cells near the hypothalamus and **induce COX-2 and the synthesis of PGE2**.
    - PGE2 enters the hypothalamus and raises the set point for the body temperature. The mechanism is unknown; however it has recently been demonstrated that in mice EP3 receptors are involved. Signals from the hypothalamus to the vasomotor center that lead to **superficial vasoconstriction**, which reduces heat loss, and induce shivering and elevate metabolic rate in the liver, which increase generation of heat.
  + **NSAIDs** prevent or reverse fever by inhibiting prostaglandin synthesis in the hypothalamus.
    - **No effect** on normal temperature
      * \*\*Effectively treat fever, but not hyperthermia (develop this in an environment where the temperature is too high or its too humid so you cant lose heat through sweating)
    - **No effect** on temperature elevated by exercise (hyperthermia)
    - **No effect** on temperature elevated by **exogenous** prostaglandins (slight fever can be seen as side effect of use of prostaglandins)
* ***TREATMENT OF INFLAMMATION*** 
  + Inflammation is a complex process in which both **prostaglandins** and **leukotrienes** play important roles. Inflammation can be
    - **Acute** 
      * Infections, tissue injury, ischemia, gout etc.
    - **Chronic** --inflammatory diseases such as
      * **Rheumatoid arthritis**
      * **Osteoarthritis**
      * **Ankylosing spondylitis**
      * asthma
      * inflammatory bowel disease (Crohn’s Disease, U.C.)
      * multiple sclerosis.
  + **1) TNF**α **and NF-****B** 
    - **Tumor necrosis factor**  plays a key role in propagating inflammation. TNFα is a protein produced by macrophages following stimulation by various agents such as lipopolysaccharide (LPS, or endotoxin) produced by **gram negative bacteria**. TNFα binds to specific receptors on a variety of cell types and activates a transcription factor called ***nuclear factor*** ***B*** (NF-B) which then enters the nucleus and switches on the synthesis of many proinflammatory proteins.  These include:
      * Cyclooxygenase 2 (Cox-2)
      * 5’-lipoxygenase (5’ LO) and its activator protein (FLAP)
      * Phospholipase A2
      * Adhesion molecules in leukocytes and endothelial cells to promote binding of leukocytes at the site of inflammation
      * TNF and interleukin-1IL-1to amplify and propagate the process.
    - Activation of NF-B results when an **inhibitor protein** called I-B is phosphorylated by a specific protein kinase and degraded. The net effect is an increased synthesis of prostaglandins and leukotrienes.
  + **2) EFFECTS OF EICOSANOIDS CONTRIBUTE TO THE SYMPTOMS OF INFLAMMATION** 
    - Redness (Erythema) - PGE2, PGI2 induce vasodilation
    - **Edema** - LTC4, LTD4 induce contraction of vascular endothelial cells -  enhanced by vasodilation
    - **Pain/Tenderness** - PGE2, PGI2, LTB4
    - Infiltration by Leukocytes - LTB4 is a potent chemotactic factor for leukocytes It induces expression of adhesion proteins in both vascular endothelial cells and neutrophils. It also promotes activation of leukocytes.
  + **3) NSAIDS**
    - Inhibit prostaglandin synthesis, but may also have other anti-inflammatory actions. They alleviate symptoms of rheumatoid arthritis and osteoarthritis, but do not alter the course of the disease.
      * Much higher doses of aspirin (3-8 g aspirin/day, 0.15-0.30 mg/ml) and other NSAIDs are needed to treat inflammation than are necessary for simple analgesia. WHY?
        + When we treat inflammation we find we need higher levels of drug than would be needed for treatment of pain.
      * Inflammation is a complex process and the beneficial effects of various NSAIDs may be dependent on effects in addition to inhibition of COX, e.g., **suppression of induction of COX-2**, inhibition of migration of neutrophils and macrophages, and adherence of granulocytes to damaged endothelium, etc. It has been reported that aspirin and salicylic acid inhibit the kinase that phosphorylates I-B and hence inhibit activation of NF-B.
        + COX2—this is the inducible form of COX and THIS DRIVES INFLAMMATION as far as the PG’s are concerned and THIS IS BLOCKED BY NSAIDS
      * Rheumatoid arthritis and osteoarthritis require prolonged treatment (b/c it is a chronic disease so you need to take these all the time) at higher doses with NSAIDs and, consequently, these patients are at the **greatest risk for adverse GI effects** (see below). These patients are therefore likely to benefit the most from using drugs that **selectively inhibit COX-2** than for COX-1 b/c the assumption is that COX1 is more associated with the side effects that we want to avoid.
        + Newer NSAIDs usually preferred, because have less intense side effects (e.g. meloxicam)
        + COX-2 selective NSAIDs: **CELECOXIB** (1998) and **ROFECOXIB** (1999) became available
* ***PROPHYLAXIS OF THROMBOSIS***
  + TXA2 and PGI2 play important and opposing roles in the **vascular system**.
    - TXA2 synthesized by platelets, contracts vascular smooth muscle and promotes aggregation of platelets.
    - PGI2 (prostacyclin) synthesized by endothelial cells relaxes vascular smooth muscle and inhibits aggregation of platelets.
  + **ASPIRIN PREVENTS HEART ATTACKS AND STROKES**



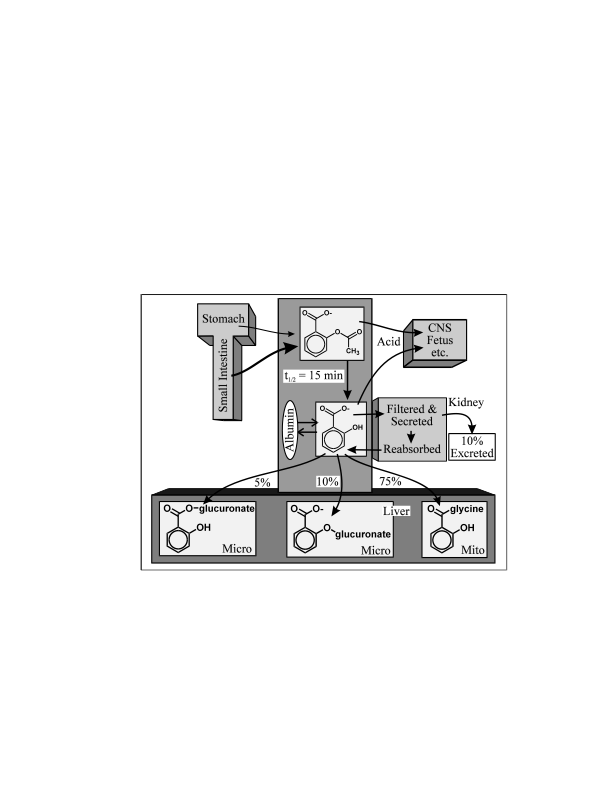
* + - NSAIDs **inhibit platelet aggregation** by blocking platelet COX-1 dependent thromboxane synthesis.
    - **Aspirin is unique in that it irreversibly** and potently inhibits platelet COX-1 at relatively low doses **(< 75 mg aspirin)**.
      * Inhibition persists for the life of the platelet, since platelets cannot synthesize proteins to reverse the effect of inhibition by aspirin. As opposed to endothelial cells which are making proteins all the time, platelets don't have a nucleus or DNA and don't make proteins. Leads to an increased (X2) clotting time.
      * Effect is limited because other factors such as thrombin are still able to induce platelet aggregation. COX-1 in vascular endothelial cells is not significantly affected by low- dose aspirin.
        + Does NOT block thrombin-induced aggregation
    - Many have pointed out that the production of PGI2 (prostacyclin) is mostly mediated by COX-2 so this makes things more complicated because most of the drugs block both. Blocking both COX seem to tip the system to favor clotting (you would also see this to a higher degree with COX-2 selective inhibitors)
      * All other NSAIDS have a risk of thrombosis attached to them except Aspirin (this is NOT because aspirin is the only one to block COX in the platelets because others do too—aspirin just does it irreversibly)
    - **Important Note: All other NSAIDs have a black box warning, which states that they “may cause an increased risk of serious cardiovascular thrombotic events, MI and stroke, which can be fatal”.** 
      * 
    - **USES** - (Recommendations of FDA Jan ’97, Oct ’98)
      * Treatment of suspected acute MI
      * Primary prevention of arterial thrombosis in MI’s in patients who are high risk (men >50 y/o, women >65 y/o, and have no other risk factors)
        + They also were shown to help prevent ischemic stroke in all women >45 y/o
      * Patients (men and women) who have suffered heart attacks, unstable angina, ischemic strokes or mini-strokes (transient ischemic attacks) or have chronic stable angina or have undergone bypass surgery, angioplasty or other revascularization procedure.
      * Aspirin should be avoided in patients with
        + Active peptic ulcer –blocking PG synthesis in this case will be harmful
        + Hepatic or renal disease
        + Disorders of blood coagulation

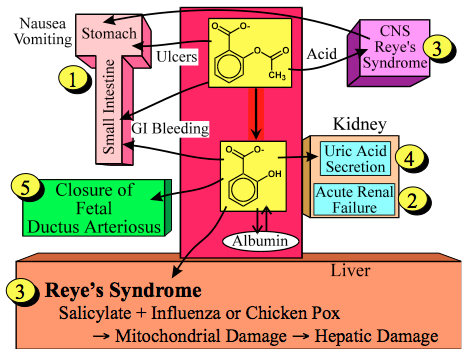
Active bleeding

Hemophilia

* + - ***IMPORTANT: Aspirin has a unique ability to inhibit platelet cyclooxygenase irreversibly even at very low doses.***
* ***CLOSURE OF THE DUCTUS ARTERIOSUS*** 
  + The *ductus arteriosus* is a blood vessel in the fetus that diverts blood from the **pulmonary artery** into the **aorta**. Prevents excessive blood flow to fetal lungs. Prostaglandins appear to play an important role in keeping the *ductus arteriosus* open/dilated during the last few weeks of pregnancy. Normally, it closes soon after birth following elevation of the O2 tension.
  + ***USE***
    - **INDOMETHACIN** is used to close the *ductus arteriosus* in neonates
  + ***SIDE EFFECT***
    - **NSAIDs** can cause premature closing of the *ductus arteriosus* if administered  during the last weeks (after 32 week) of pregnancy
  + **REVIEW: ALPROSTADIL** (PGE1, *Prostin VR Pediatric*®) is an important PG that can be used to maintain blood flow through the ***ductus arteriosus*** and keep it open in neonates.
    - Sometimes *ductus arteriosus* patencyis ideal especially when there are heart defects which prevent the normal passage of blood from the right heart to the lungs. Patent *ductus arteriosus* allows for blood to go from left heart to pulmonary arteries. Must fix the heart defect thought—keeping *ductus arteriosus* open only buys you time.
* ***TOCOLYSIS*** 
  + **PGE2 and PGF2a** induces contraction of uterine smooth muscle during pregnancy. The sensitivity increases during pregnancy and PGE2 plays a role in normal labor.
    - By blocking uterine PGE2 synthesis **NSAIDs** can delay the onset of labor.
    - **INDOMETHACIN** can be used as a “tocolytic” to delay premature labor if <32 weeks gestation, but it **is not the drug of choice**. **MgSO4** is preferred.
    - Other drugs that can delay the onset of labor include **Ca2+ channel blockers.**
    - Aspirin should be avoided in the last weeks of pregnancy to avoid excessive blood loss and the tocolytic effect.
  + **REVIEW: DINOPROSTONE** (PGE2, *Prostin* E2®, 1977) is a **vaginal suppository** for cervical ripening, evacuation of uterus after fetal death, second trimester abortion. (See “Autacoids...” notes).
    - **CARBOPROST** (PGF2a) prevent post-partum bleeding
* ***SUMMARY of THERAPEUTIC USES of NSAIDS***
  + Analgesia
  + Treatment of fever
  + Treatment of inflammation
  + Antiplatelet (Aspirin)

**PHARMACOKINETICS and ADVERSE EFFECTS of NSAIDS**

* 
* ***ABSORPTION and DISTRIBUTION OF ASPIRIN***
  + **Taken orally** and absorbed mainly in the **small intestine**, but since they are weak acids, don't get much drug absorption takes place in the **stomach** because solubility is low in acid. This may exacerbate gastric irritation.
  + **Aspirin** is unique because it has an acetyl group that can be transferred to water which lends to its irreversible action and that acetyl group comes off of the aspirin pretty quick in the blood stream which contributes to this drugs half life of 15 minutes before it develops into salicylate
    - **In blood,** 80-90% of salicylate and about 99% of most NSAIDS are bound to albumin. This can lead to drug interactions, e.g., displacement of warfarin.
  + **As lipid soluble weak acids** most of these drugs can easily cross cell membranes making them easily absorbed from the small intestines (good partition coefficient). The acid form can enter the CNS, and cross the placenta and into the fetus, etc. Excretion involves the protein bound form and free drug and in the kidney 20% of the free drug will get filtered and the protein bound drug will get secreted by the OAT in the kidney (blood🡪 interstitium 🡪 tubule) and most of the drug get reabsorbed in the kidney before it gets to the bladder. saturated
* ***METABOLISM AND EXCRETION***
  + **Aspirin** itself has t1/2 = 15 min due to action of esterases in blood and liver. The product **salicylate**, however, is also an active NSAID.
  + **Salicylate** is converted to membrane impermeant products in the liver by conjugation with glucuronic acid (15%) and glycine (75%). These products are excreted by the kidneys.
    - We only excrete about 10% of the drug by the kidney. After they are reabsorbed they get metabolized by the liver to make them more easily excreted later.
    - Salicylic acid can get glucuronidated at several positions but most of the drug gets conjugated w/ glycine in the mitochondria and excreted that way.
      * Glycine reacts with acyl-CoA derivative of the drug in the mitochondria
      * Glucuronidation occurs in the endoplasmic reticulum
    - The enzymes that metabolize these drugs in the liver can be saturated so if you as you up the dose you go from a first order elimination towards a zero order elimination leading to a longer half life of the drugs (this is what occurs when you have a chronic inflammatory disease like RA—it allows for you to take the drug less often because it is remaining in the system longer b/c of the enzyme saturation from taking higher doses for prolonged periods)
  + Much of the free salicylate filtered or actively secreted in the **kidney** is **reabsorbed** by non-ionic back diffusion; only 10% of a **normal dose at normal pH** is excreted as salicylate.
    - Note also that acidification of blood promotes distribution of the salicylic acid to CNS
  + ***IMPORTANT - especially in relation to OVERDOSE: Metabolic pathways become saturated and, hence, the half-life increases with dose from 2-3 hr for a normal analgesic dose to 12 hr for an anti-inflammatory dose and 15-30 hr for an overdose, i.e. elimination is no longer first order. Under these conditions, excretion of the salicylate anions can be increased by raising the pH of the blood/urine.***
* ***ADVERSE EFFECTS***



* + These drugs are fairly safe and well tolerated; however, because of their widespread use, the number of persons suffering adverse effects is high. Most adverse effects are related to inhibition of prostaglandin synthesis.
  + **1) GI EFFECTS**
    - **Adverse GI effects—bleeding, gastric and duodenal ulcers and perforation are the most important and frequent side effects of these drugs.** Is this the only location in the body where prostaglandins play an important role all the time? Maybe the acid alone is sufficient stress to induce their synthesis?
      * Blockage of PGE2 synthesis in the stomach by NSAIDs increases H+ and pepsin secretion and decreases mucus and HCO3- secretion.
      * With high doses, 20% of patients may suffer: dyspepsia, nausea, vomiting, damaged gastric mucosa, **increased GI bleeding** (1 ml increases to 4 ml) and **ulcers**.
      * These effects usually only cause serious problems when anti-inflammatory doses are taken over a prolonged period of time, e.g., for arthritis.
      * Combination of NSAIDs with the PGE1 analog **MISOPROSTOL** (*Cytotec*®) helps protect patients from these effects. *Arthrotec*® combines diclofenac and misoprostol in a single tablet.
      * Patients who consume large quantities of **ALCOHOL** are particularly sensitive to adverse GI effects especially bleeding. Since 1997 the FDA has required all over the counter NSAIDs to carry an appropriate warning.
  + **2) RENAL EFFECTS**
    - PGE2 and PGI2 produced by mesangial cells, medullary interstitial cells and medullary collecting duct cells in the kidney protect the function of the kidney i.e. urine production, by **dilating** renal blood vessels and **promoting H2O and salt excretion**. This is important for maintaining the function of the kidney in patients with **chronic renal disease**, nephrotic syndrome, **congestive heart failure**, **cirrhosis of the liver** (with or without ascites), **hypovolemia** etc., in which there is an increase in production of **vasoconstrictors** and renal blood flow is decreased🡪 ↓ urine production. Prostaglandins are necessary in order to maintain normal functioning of the kidneys under these pathological states. W/o them you get throw the patient into acute renal failure.
    - **Vascular Effects**
      * **PGE2 and PGI2** dilate afferent glomerular arterioles.
      * **PGI2** antagonizes effect of angiotensin II on mesangial cells and thereby **increases** GFR. It also antagonizes vasoconstrictive effect of angiotensin II on the efferent glomerular arterioles and thereby **decreases** filtration fraction and the forces driving reabsorption.
      * **PGE2 dilates medullary blood vessels—the vasa recta—**which decreases medullary hypertonicity and hence the driving force for water reabsorption
    - **Tubular Effects** 
      * **PGE2** decreases reabsorption of Na+, K+ and Cl- in thick ascending limb.
      * **PGE2** produced by macula densa cells stimulates renin release by the granular cells. Helps maintain systemic BP to maintain blood flow to kidney.
      * **PGE2** antagonizes action of antidiuretic hormone in the medullary collecting duct.
    - ***Important: Net effect is preservation of kidney function by a local effect in the face of systemic increases in levels of vasoconstrictors.*** 
      * **NSAIDs** can cause acute renal failure in some patients. By blocking renal prostaglandin synthesis, NSAIDs remove the last line of defense.
  + **3) REYE’S SYNDROME –\*\*only seen in use of salicylates like aspirin but not the other NSAIDs** 
    - This involves severe **hepatic** and **brain damage** (encephalopathy) and can occur when **aspirin** and other **salicylates** are taken by **children** infected with **influenza** or **chicken pox (varicella)**.
      * This was because they produce mitochondrial damage in the liver (mitochondria makes urea from ammonia). When your liver cant make urea from ammonia it leads to ↑ ammonia in the circulation which causes **hepatic encephalopathy**
    - Mechanism is unknown and an association with other NSAIDs has not been demonstrated. In 1980, 1207 cases were reported in the U.S. Due to warnings, this has fallen to < 36 per year since 1987.
    - Salicylates are not normally recommended for use in children. Ibuprofen and acetaminophen are approved for use in children.
  + **4) URIC ACID SECRETION** 
    - **Low doses** (1 - 2 g/day) of salicylates decrease uric acid excretion by blocking its active tubular secretion in the kidney. May produce hyperuricemia.
    - **High doses** (> 5 g/day) stimulate uric acid excretion by blocking its proximal tubule reabsorption.
    - **Intermediate doses** (2 - 3 g/day) no **net** effect is observed.
    - **All doses** block the effect of **probenecid**, which is used in treatment of gout  to increase uric acid secretion.
  + **5) CLOSING OF THE *DUCTUS ARTERIOSUS***
    - In the fetus, the *d.a.* connects the pulmonary artery and the aorta and is kept open by PGE2, closes soon after birth
    - **NSAIDS** can cause premature closing of the *d.a.* when used in the last weeks of pregnancy
    - ***Review*: INDOMETHACIN** (an NSAID) is used to close a ***patent*** ***ductus arteriosus*** in neonates
    - ***Review*:** Also remember **ALPROSTADIL** (PGE1, *Prostin VR Pediatric®,* 1981) is used to keep the *d.a.* open in neonates with heart defects
  + **6) HYPERSENSITIVITY** 
    - Observed in about 1% of general population, but in about **20%** of those with **nasal polyps** or **asthma** .
    - **Symptoms**: NSAID/aspirin induced Bronchoconstriction and shock.
    - **Treatment**: Epinephrine.
    - **Cause**: Arachadonic acid can get converted into PG’s which produce bronchodilation (like PGE2 and PGI2) or arachadonic acid can enter into LT synthesis. Because NSAIDS block PG synthesis you get ↓ in PGE2 and PGI2 and the arachadonic acid is shifted into the LT synthesis and you get increased LT synthesis.
    - ***IMPORTANT: Individuals hypersensitive sensitive to aspirin are usually also sensitive to other NSAIDs, however they are less sensitive to non-acetylated salicylates and not sensitive to acetaminophen.***
* ***TOXIC EFFECTS of SALICYLATES***
  + Due to widespread availability, accidental and intentional overdose of aspirin is not uncommon. The toxic effects of salicylic acid are correlated with the **concentration of salicylate in the blood stream.** 
    - Analgesic doses usually yield blood levels of 0.06-0.1 mg/ml, while anti-inflammatory doses yield 0.15-0.35 mg/ml and levels greater than 1.6 mg/ml can be lethal🡪Ingestion of 10-30g has caused death. 4mL of methyl-salicylate (derivative of salicylic acid found in things like bengay—topical preparations for muscles) can be fatal in children.
  + **EARLY STAGE TOXICITY (“SALICYLISM”, 0.35 - 0.5 mg/ml)**
    - These effects can be seen at **maximum therapeutic doses** and the early stages of intoxication. Metabolic pathways for salicylate conjugation saturate, therefore free levels rise and **t1/2 increases.**
    - CNS Effects (most obvious)
      * **Tinnitus—first one that you see when someone is OD. KEY INDICATOR**
      * Hearing loss
      * Vertigo
      * Emesis (CTZ) 🡪 **FLUID LOSS**
    - Kidney
      * Respiratory alkalosis is compensated by increased NaHCO3 excretion
    - Metabolic Effects
      * Salicylic acid has a delocalized charge and this allow the charged form to cross lipid membranes so if you can get the protonated and the charged form to cross lipid membranes that means this drug can transport protons across membranes. Uncoupling of mitochondrial oxidative phosphorylation which makes ATP (dependent on the H+ pump, which is driven by the electron transport chain and respiration—so the whole process really depends on the membrane being impermeable to protons so these drugs can screw this up) 🡪 loss of ATP as heat🡪 Body works harder and oxidizes more substrates through the TCA cycle🡪 leads to elevated CO2 production 🡪 **increased respiration 🡪 breathing out water 🡪 FLUID LOSS**
    - NET EFFECT = FLUID LOSS, BUT NOT SERIOUS
  + **MILD - MODERATE TOXICITY (0.5 - 0.8 mg/ml)**
    - CNS Effects
      * Stimulation of respiratory center 🡪 hyperventilation (CO2 loss) 🡪 Fluid loss (breathing out water)
        + Hyperventilation 🡪 respiratory alkalosis (CO2 loss)
        + Hyperventilation 🡪 NaHCO3 excretion by kidney 🡪 **FLUID LOSS**
    - Metabolic Effects
      * Heat production by uncoupled mitochondria 🡪 **hyperthermia (excessive heat production)** 🡪 sweating 🡪 **FLUID LOSS** 
        + Remember these drugs can be used to lower body temperature (not in hyperthermic conditions) and here they are causing hyperthermia
      * Glycolysis stimulated to make ATP (Glycogen🡪 glucose🡪 pyruvate and lactate) b/c mitochondria cant make ATP 🡪 glycogen depleted 🡪 ↓ in blood glucose🡪 **hypoglycemia**
      * Levels of CO2, lactate, pyruvate (lactate and pyruvate are from glycolysis) acetoacetate (from FA’s) rise = **“metabolic acidosis”**
  + **SEVERE TOXICITY (1.1** - **1.6 mg/ml)** 
    - CNS EFFECTS
      * **Depression of Respiration** 🡪 diminished CO2 loss 🡪 respiratory acidosis (HCO3- depleted)
    - Fall in plasma pH increases salicylic acid entry into the brain and decreases its excretion by the kidneys
    - **Coma**
  + **LETHAL TOXICITY (> 1.6 mg/ml)**
    - METABOLIC EFFECTS  Hyperthermia and associated dehydration 🡪 **Death**
    - CNS EFFECTS  Respiratory Failure 🡪 **Death**
    - KIDNEY  Dehydration, hypernatremia, hypovolemia, PG synthesis blocked 🡪 Renal Failure 🡪 **Death**
* ***TREATMENT of SALICYLATE POISONING—*treat the symptoms** 
  + GENERAL GOALS of treating the poisoned patient are 1) to maintain respiration and circulation. 2) To reduce and keep the concentration of poison as low as possible, by minimizing absorption and maximizing elimination. 3) To minimize the pharmacological and toxicological effects.
  + **TREAT SYMPTOMS - IMPORTANT**
    - Reduce Hyperthermia
      * Tepid water or alcohol sponging
    - Do **Blood Analysis** 
      * salicylate concentration
      * pH
      * electrolyte studies
      * glucose
    - Treat Dehydration and electrolyte and pH imbalances
      * **IV fluids** - maintain kidney function
  + **MINIMIZATION OF ABSORPTION** 
    - Emesis - Ipecac Syrup
    - Gastric Lavage
    - **Charcoal** 
      * Commonly used in conjunction with sorbitol
    - Laxatives - **70% Sorbitol**, Na2SO4, MgSO4
  + **ENHANCEMENT OF ELIMINATION - IMPORTANT** 
    - **Since salicylic acid is a water soluble weak acid, excretion can be enhanced by alkalinization of the urine with IV infusion of NaHCO3 (“Alkalinize Urine”)**
    - **Hemodialysis** currently recommended if plasma salicylate is above **1 mg/ml, but...** 
      * More than half of ~ 23 deaths/yr attributed to aspirin occur when salicylate conc. <100 mg/dL
      * Invasive procedure and ↑ risk of blood clots
    - No methods exist to stimulate biotransformation (cf. acetaminophen).

**UNIQUE FEATURES of SELECTED NSAIDS**

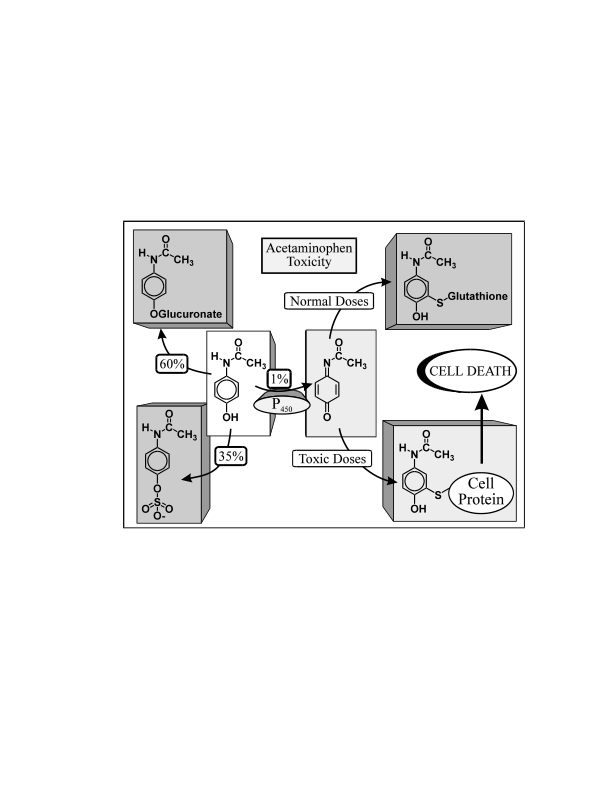
* ***SALICYLATES***
  + All the salicylates except **DIFLUNISAL** are hydrolyzed to salicylic acid.
  + **SALICYLIC ACID AND SALICYLATE** 
    - The acid is keratolytic and used topically in treatment of warts, corns, psoriasis
    - Choline salts (*Trilisate*®) and Mg2+ salts (*Doan’s*) are available.
    - Other salicylates include **SALSALATE** and **DIFLUNISAL**
    - Compared with aspirin, **salicylate** has **lower incidence of GI effects,** hypersensitivity and **no** clinical effect on **platelet function**.
  + **ASPIRIN (*Bayer*®, 1899, 1939)** 
    - Acetylates active site of cyclo-oxygenase (COX) 🡪 **irreversible** inhibition.
    - Potent anti-platelet drug for preventing MI and ischemic strokes.
  + **METHYL-SALICYLATE (Oil of Wintergreen, *Ben*-*Gay*®, *Aspercreme*®)** 
    - Absorbed through skin, commonly used as a topical NSAID
    - Very toxic if taken orally
    - Used as a flavoring
* ***ACETIC ACID DERIVATIVES AND RELATED DRUGS***
  + **INDOMETHACIN (*Indocin®,* 1965)** 
    - Potent inhibitor of cyclooxygenase-1
    - Higher incidence of GI side effects than aspirin-- Toxicity > aspirin
    - Special short term uses only, closure of ductus arteriosus in premature infants, tocolysis, acute gouty arthritis
  + **SULINDAC (*Clinoril*®, 1978)** 
    - **Prodrug** converted to active drug (sulfoxide🡪 sulfide) in the liver.
    - Undergoes **enterohepatic cycling**, prolonging action to 16 h
    - Lower incidence of GI toxicity than aspirin.
  + **DICLOFENAC (*Voltaren*®, 1988; *Arthrotec*®, 1997)** 
    - Useful for osteoarthritis and rheumatoid arthritis.
    - GI toxicity risk similar to aspirin.
    - Multiple formulations
      * Rapid release for acute pain (*Cataflam ®* K salt),
      * Extended release for arthritis (RA)
      * Ophthalmic solution (*Voltaren* ®)
      * Topical solution
      * Buffered powder for oral solution (*Cambia*®, 2009 for migraine) are available.
      * Also *Arthrotec*® combines **DICLOFENAC** and **MISOPROSTOL** (to minimize side effects in the GI tract)
  + **KETOROLAC (*Toradol*®; *Acular*®, 1989)** 
    - Used **parenterally** IV or IM for the **short-term** treatment of mild to moderate  **post-operative pain**.
    - Use for < or equal to 5 days
    - Higher incidence of GI toxicity.---only used short term
* ***PROPIONIC ACID DERIVATIVES—***lower incidence of adverse GI effects as compared to other NSAIDS
  + These drugs have a similar risk of GI toxicity as aspirin and are all available as over the counter (OTC) preparations. Useful for treatment of pain, fever, menstrual pain (dysmenorrhea) and inflammation.
  + **IBUPROFEN (*Motrin®, Advil®,* 1974, *Caldolor*®)** 
    - Half-life 1 - 2 hr
    - For analgesia 200 mg which is about equal to 650 mg aspirin, but for anti-inflammation 2.4 g which is about equal to 4 g aspirin.
    - *Caldolor*® (2009) first formulation for IV administration (injectable)
  + **NAPROXEN (*Naprosyn®; Aleve®,* 1976, 1994)** 
    - Longer half-life (t1/2 = 14 h) than ibuprofen🡪 so less frequent dosing.
  + **KETOPROFEN (*Orudis®,* 1986, 1995)** 
    - Half-life 1 - 3 hr
* ***NSAIDS WITH VERY LONG HALF LIVES***
  + Allow **once per day dosing** but take 7-12 days to reach steady state plasma concentration and both **have a higher incidence of adverse GI effects than aspirin**
  + **PIROXICAM (*Feldene*®, 1982)** 
    - Half-life = 50 hr (very long)
  + **OXAPROZIN (*Daypro*®, 1992)**
    - Half-life = 50 hr (very long)
* ***NSAIDS WITH RELATIVELY LOW COX-1 ACTIVITY***
  + **Selective for COX-2** over COX-1 (5-10-fold), hence **lower incidence of GI problems**, but not sufficient difference for FDA to allow the drugs to be promoted on this basis.
  + Used primarily as **anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis**.
  + **NABUMETONE (*Relafen*®, 1991)** 
    - Long half life ~23 hr
    - Prodrug converted to the active form in the liver
      * Methoxy-naphthyl-acetic acid (compare with naproxen)
    - Reduces exposure of stomach to active drug
    - **Lower** incidence of ulcers (#2 NSAID in ’97; #7 in ’10)
  + **ETODOLAC (*Lodine*®, 1991)**
    - Selective (~ 10x) for COX-2 *versus* COX-1
    - **Low** incidence of GI symptoms (similar to placebo) *#8 NSAID in ’10*
  + **MELOXICAM (*Mobic*®, 2000) (**#2 most frequently prescribed NSAID IN 2010)
    - Structurally related to piroxicam, long t1/2 ***but…***
    - Selective (~ 10x) for COX-2 *versus* COX-1
    - **Lower** incidence of GI symptoms (17%, placebo, 20% meloxicam, 28% diclofenac)
* ***CYCLO-OXYGENASE-2 (COX2) SELECTIVE INHIBITORS***
  + Three drugs that are several hundred fold more selective for COX-2 over COX-1 were approved by the FDA. In treatment of arthritis, these drugs appear to cause less GI damage without loss of analgesic or anti-inflammatory activity.
  + **CELECOXIB (*Celebrex*®, 1998), ROFECOXIB (*Vioxx*®, 99-04) VALDECOXIB (*Bextra*®, 01-05)**
    - Currently **CELECOXIB** is approved for treatment of
      * Rheumatoid arthritis and osteoarthritis
      * Acute pain and menstrual pain
      * Reduction in number of polyps in ***familial adenomatous polyposis –*THIS INDICATION WAS REMOVED IN 2011**
    - Selective for COX-2 over COX-1 (300-400 fold)
    - No effect on platelet aggregation
    - Claim to have minimal adverse GI side effects, and no effect on platelets while maintaining efficacy similar to naproxen, diclofenac and ibuprofen on pain
      * Original clinical trials: Ulcers observed endoscopically:
        + celecoxib 3-7%
        + naproxen 16-35%\*
        + ibuprofen 23%\*
        + diclofenac **10%** and 15%\*
      * **FDA ruled, however, that they needed to demonstrate a decreased *frequency of clinically serious GI events compared to* other NSAIDs *in well-controlled studies***
      * Result: **complicated and symptomatic ulcer rates** at 9 months for all patients, and ***those over 65 y.o*** celecoxib alone 0.78%, ***1.4%;*** celecoxib +ASA 2.19%, ***3.06%***
      * Warning of GI toxicity is still included on label
    - Risk of adverse GI toxicity has been shown for **rofecoxib** to be significantly less than for **naproxen (see VIGOR study below)**
    - Renal effects appear to be similar to other NSAIDs, remember COX-2 is found constitutively in the kidney macula densa and TAL of the loop of Henle
  + **CELECOXIB (*Celebrex*®, 1998)**
    - Celecoxib is a **sulfonamide** and should not be taken by patients who are  allergic to this class of drugs
    - Metabolized by CYP 2C9, which is inhibited by many drugs including cimetidine, zafirlukast, omeprazole, sulfonamides and ketoconazole. Also it inhibits CYP 2D6. **Hence, potential for drug interactions**
    - Half-life 11.2 hours and can be administered once per day for osteoarthritis
    - It was the 27th most frequently prescribed drug in the U.S. in 2004 and the 90th in 2010
  + **ROFECOXIB (*Vioxx*®, 1999-2004)** 
    - It is **not a sulfonamide**
    - Safety compared with naproxen “**VIGOR” STUDY** 
      * Rofecoxib 50 mg *vs* Naproxen 1000mg /day for nine months, 8076 patients with RA, mean age 58 yr, patients requiring low-dose aspirin were excluded
      * **GI SAFETY:** Incidence of ulcers, gastric perforation, upper GI bleeding, etc
        + Naproxen 121/4029
        + Rofecoxib 56/4047
        + Relative risk of symptomatic adverse GI effects = 0.46
      * **Car**d**iovascular safety:** Incidence of sudden death, MI, UA, ischemic  stroke, TIAs, peripheral venous or arterial thrombosis
        + All end points

Naproxen 19/4049 Rofecoxib 45/4047

* + - * + Non-fatal MI

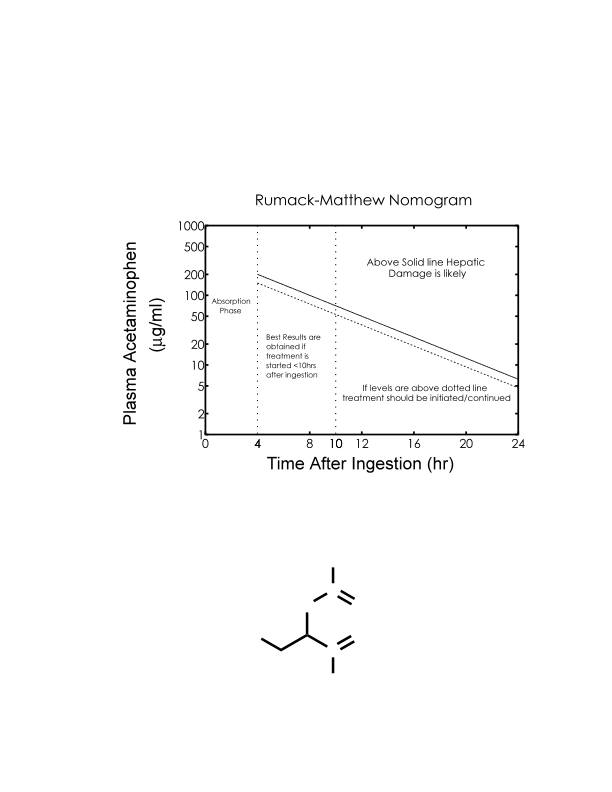
Naproxen 4/4049 Rofecoxib 18/4047

* + - * + **There is a higher incidence of serious cardiovascular thrombotic events in patients taking rofecoxib versus those taking naproxen or as it turns out placebo – removed from market by Merck 2004**
    - Rofecoxib was the 56th most frequently prescribed drug in the U.S. in 2004
  + **VALDECOXIB (*Bextra*®, 2001-2005)** 
    - Note that like celecoxib, valdecoxib is a **sulfonamide** and should not be taken by patients who are allergic to this class of drugs
    - PROBLEMS
      * Potentially fatal skin reaction which are unpredictable
        + Fatalities due to Stevens-Johnson syndrome
        + Toxic epidermal necrolysis have been reported, watch out for skin rash developing in 1st two weeks
      * Contraindicated for the treatment of postoperative pain following CABG surgery due to increased risk of CV thrombosis, death due to MI, stroke, DVT, PE ↑, in addition to risks similar to those associated with rofecoxib
    - It was the 62nd most frequently prescribed drug in the U.S. in 2004, but because of above problems was removed from the market April 2005
    - ALL NSAIDS CARRY A WARNING THAT THEY MAY ↑ CARDIOVASCULAR RISKS (except aspirin) AS WELL AS GI RISKS
      * Why do we still have Celebrex (**CELECOXIB)** still on the market? Celebrex effects COX and also inhibits calcium uptake by the SM (either by inhibitory effect on Ca channels or activating effect on K channel which regulate the Ca channel)🡪 vasodilatory effect 🡪 ↓ CV risks
* ***ACETAMINOPHEN***
  + ***IMPORTANT Acetaminophen is NOT AN NSAID, it only shares the antipyretic and analgesic properties of NSAIDs. IT DOES NOT POSSESS CLINICALLY USEFUL ANTI-INFLAMMATORY PROPERTIES.***
  + Acetaminophen is a unique drug; however, due to the fact that it has analgesic and antipyretic properties similar to aspirin and other NSAIDs, it is useful to compare their properties.
  + **PROPERTIES - SIMILAR to ASPIRIN** 
    - **Analgesic –** the combination drug hydrocodone + acetaminophen (Vicodin®) is the most frequently prescribed drug in the US
      * Note: Often prescribed in combination with opioids, e.g. acetaminophen + hydrocodone = *Vicodin*®
    - Antipyretic (↓ fever)
    - No tolerance or physical or psychological dependence develops
  + **PROPERTIES that DIFFER from ASPIRIN** 
    - Very little anti-inflammatory effect
    - No CNS effects
    - No association with Reye’s syndrome
    - No cardiovascular or respiratory effect
    - No gastric irritation (as compard to NSAID)
    - No effect on platelets (does not block platelet aggregation)
    - No effect on uric acid secretion  The reasons for these similarities and differences have not been well established.
  + **PHARMACOKINETICS** 
    - Taken orally
    - Absorbed rapidly
    - Peak plasma concentration achieved in about 1 hr. Half-life approximately 2 hr. These are similar to the properties of aspirin
  + **TOXICITY of ACETAMINOPHEN OVERDOSE**
    - Although acetaminophen has very few adverse side effects and is generally regarded as a “safe drug”, overdoses are not uncommon and can cause severe **hepatic damage**. Toxicity is expected at doses exceeding 7.5 g (adult) and doses of 20-25 g can cause **death**. In contrast to the toxic effects of aspirin, these effects are directly related to the **metabolism** of acetaminophen.
      * Low doses (< 150 mg/kg) have few side effects
        + Therapeutic doses (3g/day max) **normally** have no adverse effects
      * Single dose 7.5 - 15 g 🡪 **hepatotoxicity** (necrosis)
        + Packaging now says severe liver damage may occur if take > 4g in 24 hours
      * Single dose 20 - 25 g 🡪 potentially fatal
        + Acetaminophen toxicity is related to the metabolism of the drug



The parent acetaminophen molecule gets metabolized by conjugation w/ glucuronic acid (glucuronidation (60%)), 35% gets conjugated with sulfate group. Both of these products are harmless and inactive. CYPP450 system can metabolize it into a quinone structure which acts as an electrophil (likes electrons) and so this reacts with glutathione (glutathione reacts with electrophils—it is an antioxidant) to produce the glucuronidated harmless product. But when these conjugation enzymes get saturated (with ↑ drug) you get more drug going through the CYPP450 oxidation which consequently will deplete the levels of glutathione🡪 reactive molecule now can react with proteins that have SH groups (mitochondria for ex have proteins that transport phosphate and these have SH groups and it can react with these and inhibit them)🡪 Death of cells in the liver🡪 if you kill enough of them you can get liver damage and death

* + **METABOLISM OF ACETAMINOPHEN IN THE LIVER**
    - **At normal doses,** acetaminophen is conjugated to
      * glucuronate 60%
      * SO4- 35%
      * cysteine 3%
      * All of these yielding water-soluble, non-toxic products excreted by the kidneys. A small % undergoes P450-mediated N-oxidation (CYP 1A2, **2E1** and 3A4), yielding a product that reacts with thiol (-SH) groups. **At normal doses,** this product reacts with **glutathione** to produce a non-toxic product.
    - **At high doses** - glutathione becomes depleted and the toxic intermediate reacts with **cell proteins**, etc. This is **IRREVERSIBLE** and leads to cell death and **tissue necrosis**.
    - **Alcoholics and heavy drinkers** (> 3 per day) have a lower threshold for toxicity due to the induction of P450 enzymes and depletion of glutathione.
      * **Ethanol** can induce P450 enzymes which metabolize things like acetaminophen so you can ↑ amount of reactive oxidative intermediate
      * **Ethanol** also depletes glutathione so further limiting the elimination of the reactive intermediate
    - **Treatment** - **N-ACETYLCYSTEINE (*Mucomyst*®, *Acetadote*®)**
      * Antioxidant drug. It is a thiol (- SH) compound, provides an alternative substrate for the toxic intermediate and helps restore levels of glutathione (see below).  **IT CANNOT REVERSE DAMAGE ALREADY DONE**.
      * Give it <10 hrs after OD to minimize damage
  + **EFFECTS OF ACETAMINOPHEN TOXICITY**
    - Symptoms are relatively MILD in DAYS 1-2
      * **Stage 1**. (0-24 hr after ingestion) Symptoms are **mild** and include GI irritation, pallor, lethargy and diaphoresis (perspiration).
      * **Stage 2**. (24-48 hr after ingestion) There may be a **deceptive lack of symptoms**, but a small increase in serum hepatic enzymes may be evident.
    - HEPATIC DAMAGE SYMPTOMS in DAYS 2-3
      * **Stage 3**. (72-96 hr after ingestion)
        + Stage 1 symptoms return, but more severe and can progress to coma.
        + There is also a large increase in serum hepatic enzymes (plasma transaminases), bilirubin may be elevated and blood-clotting time (PT) may increase—b/c clotting factors are made by the liver
    - WITHOUT TREATMENT
      * **Stage 4.** (4 days - 2 weeks) Recovery phase - **if the patient survives**, permanent liver damage is rare. Acetaminophen poisoning accounts for 30-60 deaths per year in the U.S.
      * Most recover - liver regenerates (weeks/months)
      * 10% 🡪 Severe liver damage
      * 1 - 2% 🡪 Die of liver failure
    - ***IMPORTANT point here is that proteins are irreversibly damaged in the first few hours following overdose, but the symptoms are relatively mild in first day or so, i.e. by the time the victim feels bad it can be too late for treatment to be effective.***
    - Note that on 1/13/2011 in an attempt to reduce incidences of overdoses the FDA announced that combination products (opioids +acetaminophen) would be limited to 375 mg acetaminophen with transition phased in over 3 years to prevent shortages.
  + **TREATMENT OF ACETAMINOPHEN TOXICITY**
    - **Treatment** - **N-ACETYLCYSTEINE (*Mucomyst*®, *Acetadote*®)**
      * Antioxidant drug. It is a thiol (- SH) compound, provides an alternative substrate for the toxic intermediate and helps restore levels of glutathione (see below).  **IT CANNOT REVERSE DAMAGE ALREADY DONE**. Give it ASAP <8-10 hrs after OD to minimize damage. Cease treatment only if it is discovered that patient is not at risk. Most frequently used specific poisoning treatment (16K)
    - ***BLOOD ANALYSIS - ESTIMATION OF TOXIC EFFECTS***
      * **Rumack-Matthew Nomogram** (below) is used to determine if the patient is at risk based on the concentration of acetaminophen in the blood and time after ingestion.
      * Toxic levels are associated with an **increase in half-life**
      * Note: patients who have > 300 mg/l at 4 hr have 50% mortality rate



Monitoring the acetaminophen toxicity

1st order elimination on log scale is a linear line

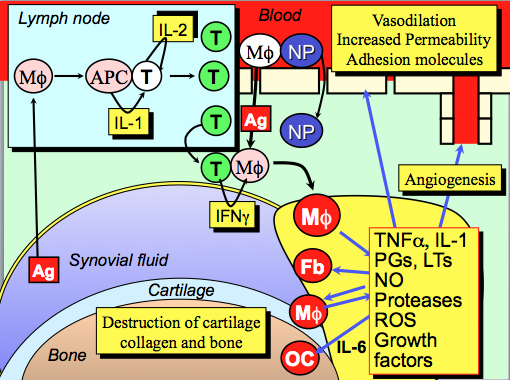
During absorption phase you can use gastric lavage to treat OD—may not be that useful

* + - ***MINIMIZATION OF ABSORPTION***
      * Useful if < 4 hr after ingestion
        + emesis (?)
        + gastric lavage (yes)
        + charcoal (no)
        + purgation (?)
    - ***ENHANCEMENT OF ELIMINATION - BY ENHANCING BIOTRANSFORMATION WITH N-ACETYLCYSTEINE***
      * MECHANISM
        + **Reacts with the toxic product**
        + Repletes glutathione
        + But does **not** reverse interaction
        + Use as soon as possible, as beneficial effects are only seen if treatment initiated < 8-10 hr after ingestion
    - ORAL THERAPY *(Mucomyst*®)
      * Dosage: 140 mg/kg loading dose followed by 70 mg/kg every 4  hr for 17 doses
        + Loading dose then give it regularly
      * SIDE EFFECTS
        + Nausea/vomiting 50%
        + Diarrhea 35%
    - IV THERAPY (*Acetadote*®, 2004)
      * Dosage: 150mg/kg/15min, 50mg/kg/4hr, 100mg/kg/16hr
        + Loading dose then give it regularly
      * IV use was not approved in the U.S. until Feb 2004
      * SIDE EFFECTS - within first 2 hr
        + **Anaphylactoid reactions 17%**

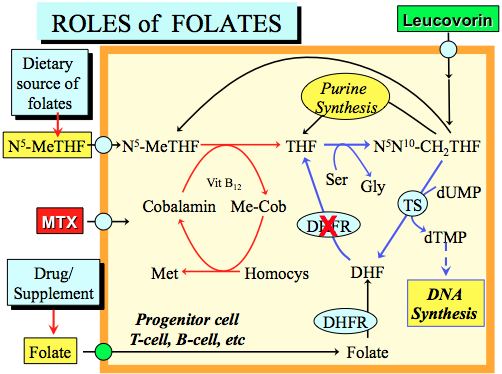
May spontaneously resolve, may need treatment. Use with caution in asthmatics, has caused a death—if they get this you have to stop therapy and give them anti-histamines/epinephrine and if they recover then you can try it again and hope they don't get it again.

* + - * + Nausea/vomiting 10-15%  Useful if patient is in a coma, or vomiting, or charcoal has been used.
    - ***IMPORTANT: Begin N-acetylcysteine therapy immediately if there is doubt about time of overdose - do not wait for results of blood tests. Only cease treatment if it is found the patient is not at risk.***

**IMMUNOSUPPRESSANTS USED IN THE TREATMENT OF RHEUMATOID ARTHRITIS**



^^Discussed in NSAID LECTURE

* Immunosuppressive drugs, such as methotrexate, azathioprine, the antimalarial chloroquine and gold compounds, which are used in the treatment of rheumatoid arthritis are often referred to as DMARDs (**d**isease **m**odifying **a**nti**r**heumatic **d**rugs). Not only do they alleviate symptoms, they also slow the degeneration of the cartilage and bone that occurs in rheumatoid arthritis. Unlike the classical NSAIDs, they are not analgesics or antipyretics. Moreover, beneficial effects are often not seen for several weeks and their use is frequently accompanied by serious side effects, which can limit the duration of treatment.
* ***CYTOTOXIC DRUGS*** 
  + Drugs that block DNA, RNA and protein synthesis and thereby block cell proliferation, e.g. of T-cells, B-cells and tumor cells.
    - These drugs inhibit cell division so it really effects organs where there is regeneration/cell division a lot—like the liver, GI tract, hair growth, bone marrow, pregnancy
    - This is the mechanism of both the beneficial effects and many of their side effects.
  + **METHOTREXATE (generic, 1953)**
    - Methotrexate appears to have a better benefit /risk ratio than the other immunosuppressant and is currently the drug of choice for treatment of rheumatoid arthritis. (See notes on *Antineoplastic Drugs*)
      * Anti-inflammatory doses are given orally (7.5 mg once per week)
      * Used in treatment of rheumatoid arthritis, asthma, Crohn’s disease and multiple sclerosis, psoriasis
    - ***USES***
      * **Treatment of choice for Rheumatoid arthritis**
        + Benefit/risk ratio better than other DMARDs
        + Administered orally for RA, 1x per week
      * Multiple sclerosis, Crohn’s disease, asthma, psoriasis
      * Cancer
    - ***TOXICITY***
      * Bone marrow, GI tract, liver, fetus
      * **Contraindicated in pregnancy – category X**
        + Avoid pregnancy for 6 months after cessation of therapy
      * **Toxicity can be offset by folic acid and by “leucovorin rescue” without decreasing efficacy. How?** Take those thing 24 hrs after initial dose of MTX. Your trying to protect all the cells that aren’t dividing as fast as the T-cell and B-cells and cancer cells. The rapidly dividing cells need more THF than normal cells so they will be more sensitive to this process.
    - ***MECHANISM***
      * It is an analog of folate and it Inhibits dihydrofolate reductase (DHFR), which converts DHF to tetrahydrofolate
        + Interferes with folate metabolism
      * Lack of tetrahydrofolate blocks purine synthesis and the conversion of dUMP (uracil) to dTMP (thymine)—remember DNA Doesn't use uracil it uses thymine, consequently DNA, RNA and protein synthesis are inhibited
        + Interferes with purine synthesis
      * Net Effect: Inhibition of cell proliferation (cancer cells, bone marrow, B-cells, T-cells, etc.)
        + 
    - ***ROLE OF FOLATES AND VITAMIN B12***
      * THFs are involved in DNA & RNA SYNTHESIS
        + Synthesis of purine bases (adenine and guanine)
        + Conversion of dUMP to dTMP used in DNA synthesis (uracil moiety to thymine moiety) – (this enzyme thymidylate synthase is blocked by 5’Fluoro-uracil)
        + Big difference between these two processes is that U to T conversion produces DHF, while other functions regenerate THF
        + DHF must be converted back to THF by DHF reductase - this is inhibited by Methotrexate
        + Folates will be trapped as DHF, so purine synthesis will also be blocked
      * Where does THF come from?
        + 1) From the diet – dependent on vit B12

Major dietary form is N5-Me-THF

Folate from the diet🡪 N5-Methyl-THF 🡪 into cells but not useful substrate it doesn't donate the methyl group to important reactions so vitamin B12 (Cobalamin) removes that methyl group and uses it to convert homocysteine into methionine

Methyl group is removed by transfer to cobalamin (Vit B12) to produce methyl-cobalamin and subsequent transfer to homocysteine to produce methionine

Consequences of deficiency in vit B12 (cobalamin)

Deficiency of THF – it is “trapped” as N5-Me-THF

Homocysteine accumulates

So vitamin B12 is important to the utilization of dietary folate

So vitamin B12 deficiency will ↓ DNA synthesis

* + - * + 2) From conversion of folic acid supplements to THF by DHF reductase

***Consequence:*** for nucleotide synthesis, folate can bypass need for vitamin B12 – not true for nerve damage

* + - * Other important information
        + Methotrexate is taken up into cells by the folate transporter
        + Like folate, becomes polyglutamated to keep it within the cells, which increases potency and traps the drug in the cell prolonging its duration of action,
        + Effect of methotrexate can be reversed by “leucovorin rescue”

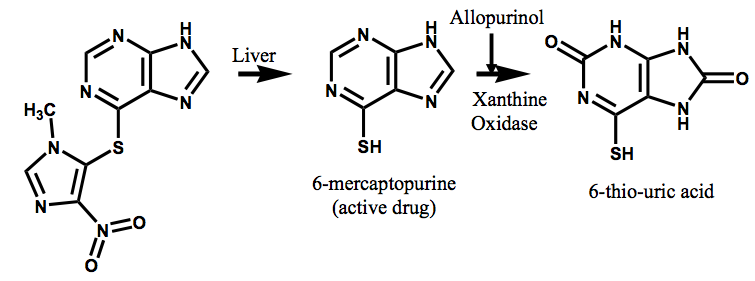
Leucovorin administered 24 hr after high-dose or **low-dose** methotrexate

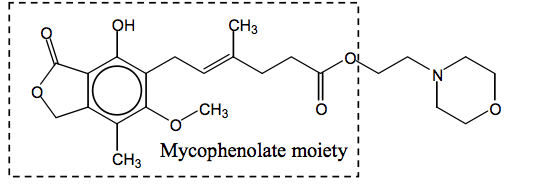
Taken up by folate transporter - competes with MTX

Bypasses need for dihydrofolate reductase, THF↑

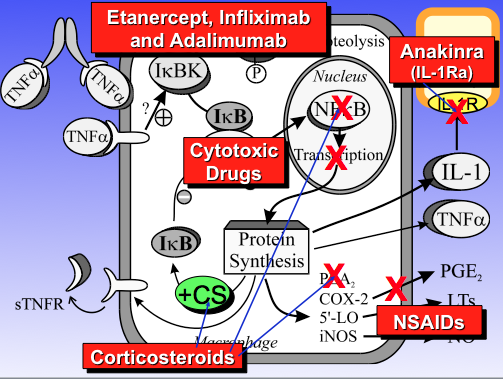
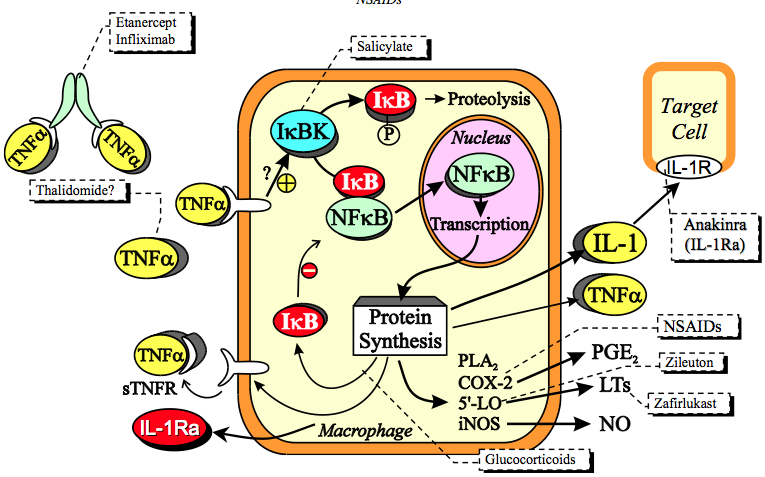
Allows slow DNA, RNA and protein synthesis

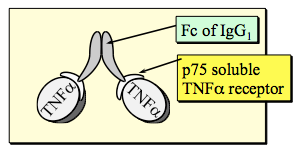
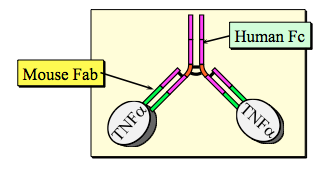
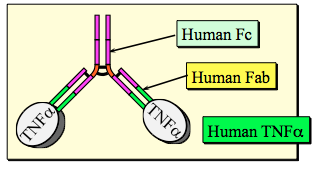
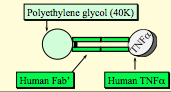
* + **LEUCOVORIN (N5-formyl THF, *Wellcovorin*®, 1952)** 
    - Administered 24 hr after high-dose methotrexate to reduce their side effects
      * ↓ side effects of MTX without really ↓ its effectiveness
    - Taken up by reduced-folate transporter competes with methotrexate
    - Converted to N5,N10 methylene-THF and bypasses need for dihydrofolate reductase
    - Allows DNA, RNA and protein synthesis at a slow rate
    - *Review:* **Potentiation (↑ effectiveness) of Fluorouracil Therapy (anticancer drug)** 
      * dUMP + N5,N10 methylene-THF (needs the methyl group from THF) 🡪 dTMP
      * With Fluorouracil, FdUMP is formed then,
        + FdUMP + leucovorin blocks thymidylate synthesis
  + **AZATHIOPRINE (*Imuran*®, 1968)**
    - Has been a very important drug in preventing rejection in renal transplants.



* + - * *Activation of azathioprine. Azathioprine is converted to the active drug, 6-mercaptopurine in the liver. One of the steps in its metabolism is the conversion to 6-thio-uric acid by xanthine oxidase, which can be blocked by allopurinol (see below).*
    - ***MECHANISM***
      * Prodrug converted to **6-mercaptopurine (in the liver),** which blocks DNA and RNA synthesis
      * The 6-MP has a purine on it and gets metabolized by Xanthine oxidase into thiouric acid (precursor in the production of uric acid in the manifestation of gout)
    - ***TOXICITY***
      * Toxic to rapidly growing cells: bone marrow, GI tract, and fetus (category D—means can be prescribed when the benefits to the patient outweight the risks to the fetus)
    - ***DRUG INTERACTION***
      * **Allopurinol** blocks xanthine oxidase and allows accumulation of 6- mercaptopurine – potentiates toxicity
        + This drug is used in treating gout
        + If you do use these drugs together you need to ↓ dose down to about 1/3rd of what you were going to use
      * If allopurinol used, dose of azathioprine must be lowered
    - ***USES INCLUDE***
      * Treatment of severe RA, IBD, lupus nephritis, Wegener’s granulomatosis, as well as prevention of rejection of **renal transplants**
  + **LEFLUNOMIDE (*Arava*®, 1998)**
    - A prodrug drug approved for the treatment of rheumatoid arthritis.
    - ***MECHANISM***
      * Prodrug converted to active form in gut or liver
      * Inhibits dihydro-orotate dehydrogenase an enzyme catalyzing a key step in pyrimidine synthesis, thus blocks RNA and DNA synthesis.
        + Its structure only have one ring (like pyramidines) so it makes sense that it is interfering with their synthesis
      * Has a **long half-life** (2 weeks) due to entero-hepatic cycling
        + Entero-hepatic cycling—conjugated in the liver🡪 secreted in bile🡪 bile goes to the colon where it is cleaved by bacterial enzymes🡪 gets reabsorbed back into the body
        + To eliminate this drug from the body 5 half lives so 5 x 2 weeks = 10 weeks
    - ***TOXICITY***
      * Liver toxicity (7%) > methotrexate - Monitor liver enzymes (ALT x2 normal then stop therapy and use cholestyramine)
      * Teratogenic - Should not be used if there is a possibility of pregnancy  (category X)
      * **CHOLESTYRAMINE** (see *Antilipemics*) can be used to shorten half-life to 1 day b/c it BLOCKS ENTERO-HEPATIC CYCLING
  + **GOLD COMPOUNDS: AURANOFIN (*Ridaura*®, 1985) AUROTHIOGLUCOSE (*Solganal*®)**
    - ***GOLD THERAPY OR “CHRYSOTHERAPY” THERAPY FOR RA.***
      * Due to toxicity, use is reserved for cases in which response to standard therapies (NSAIDs, MTX) is inadequate.
        + Early active RA, if inadequate response to NSAIDs
      * **AURANOFIN**: Oral administration  Deacetylated in GI tract, only 25% absorbed
      * **AUROTHIOGLUCOSE**: IM administration  Water soluble, higher plasma levels obtained
    - ***MECHANISM***
      * Mechanism unknown - may inhibit **macrophages?** 
        + Suppresses immune response
      * Long half life - blood 26 days, tissues 80 days
    - ***ADVERSE EFFECTS—HIGH INCIDENCE*** 
      * Diarrhea, vomiting etc. (47%--if taken orally), rash (24%)
      * Stomatitis (13%)—ulcers in the mucous membranes of the mouth
      * Renal toxicity (glomerulitis, proteinuria, hematuria)
      * Blood dyscrasias—bone marrow toxicity e.g. thrombocytopenia
      * IM *versus* Oral Administration
        + Except for GI side effects, incidence of side effects is higher  for IM administration
        + IM administration of **AUROTHIOGLUCOSE** also leads to gray/blue pigmentation of skin at injection site especially if exposed to light
  + **HYDROXYCHLOROQUINE (*Plaquenil*®, 1955)**
    - Antiinflammatory (~400 mg/day)
    - Also an Antimalarial (400 mg/wk) drug
    - ***MECHANISM***
      * Mechanism not established, max effect takes 3-6 months
    - ***USES*** 
      * Chronic discoid and systemic lupus erythematosus
      * RA, if not responsive to other therapies
    - ***TOXICITY*** 
      * Danger of **irreversible retinal damage** - monitoring necessary every 6-12 m
  + **D-PENICILLAMINE (*Cuprimine*®, 1970; *Depen*®, 1978)**
    - Chelating agent for Cu, Hg, Zn, Pb poisoning
    - ***USE*** 
      * Oral, for severe active RA, if unresponsive to less toxic therapy
      * Cu, Hg, Pb poisoning
      * Wilson’s disease--↑ copper in the liver
      * Cystinuria (genetic)🡪 ↑ cysteine (normally reabs in the kidney but in this they don't have normal transporters)🡪 urinary tract stone- treat if >300 mg/d
    - ***TOXICITY - MORE TOXIC THAN GOLD COMPOUNDS*** 
      * Cutaneous lesions
      * Bone marrow toxicity - may be fatal -monitoring necessary
      * Autoimmune syndromes, e.g. Myasthenia gravis can develop in these patients
  + **MYCOPHENOLATE MOFETIL (*CellCept*®, 1995) MYCOPHENOLIC ACID (*Myfortic*®, 2004)**
    - This drug is a little more selective for inhibiting guanine synthese (a purine)
    - Mycophenolate inhibits the ***de novo*** synthesis of dGMP and hence synthesis of RNA and DNA.
      * Since T-cells and B-cells are **dependent** on ***de novo*** synthesis of guanine—they can recycle broken down nucleotides, they are more sensitive to this cytotoxic agent than other cell types that can utilize the salvage pathway.
        + So because of the fact that T-cell and B-cells need de novo guanine synthesis, this drug is especially good at limiting their proliferation. So blocks T-cell and B-cell proliferation as well as the ability of memory B-cells to make antibodies b/c it blocks RNA synthesis, and it blocks lymphocyte adhesion and migration—because they cant produce the proteins they need for this function
    - 
      * *Fig. 7 Mycophenolate mofetil is a prodrug. The ester is hydrolyzed “immediately” after oral or IV administration releasing the active drug - mycophenolate*
    - ***USES***
      * Kidney, heart and liver transplant rejection prophylaxis in combination with cyclosporine and corticosteroids
      * Off label use to treat Rheumatoid arthritis (non-FDA approved)
    - ***MECHANISM*** 
      * Mycophenolate mofetil rapidly hydrolyzed to MPA (mycophenolate)
        + Oral or IV
      * Reversible but non-competitive inhibition of IMP (inosine monophosphate) dehydrogenase, the rate limiting step in GMP synthesis.
      * Blocks proliferation, adhesion and migration of T and B cells, and antibody production by B cells
    - ***ADVERSE EFFECTS –RELATIVELY FEW*** 
      * **GI effects** –diarrhea vomiting are the most common >10% patients
      * Bone marrow toxicity is **less than azathioprine**
      * **Nephrotoxicity minimal** (contrast cyclosporine)
      * **Pregnancy category D** (need pregnancy test, reliable contraception)
        + Can be used if benefits to the patient out weight risks to the fetus

**AGENTS THAT TARGET TNFα AND INTERLEUKINS**—Suppression of immune and inflammatory response in autoimmune/inflammatory diseases



* ***GLUCOCORTICOIDS***
  + (See sections on *Steroids* and the *Treatment of Asthma and COPD*). Natural antagonists for TNFα. These drugs are important in the short-term treatment of flare-ups of rheumatoid arthritis, but are not very useful for the long-term treatment of RA and other chronic inflammatory diseases due to toxic side effects. They also played a key role in making kidney transplants possible in the 1960’s--↓ rejection
  + ***MECHANISM***
    - Switch on synthesis of I-B, and hence inhibit activation of NF-B
    - Active corticosteroid receptors block action of NF-B
    - Switch on synthesis of lipocortins which inhibit PLA2
    - Inhibit proliferation of inflammatory cells--Block expression and actions of TNFα and IL-1
* ***DRUGS THAT TARGET TNF*α**
  + The relatively new drugs etanercept and infliximab and adalimumab selectively target TNF. They have proven very beneficial to patients with rheumatoid arthritis who are resistant to methotrexate - the standard therapy for severe RA. They are usually used in combination with methotrexate.
  + ***INDICATIONS***
    - Rheumatoid arthritis – moderate-severe (these patients are usually on MTX already)
      * Reducing signs and symptoms of RA
      * Inhibiting the progression of structural damage
      * Improvement of physical function
      * ***Note:*** MTX inhibits anti-drug antibody production that usually develop with the use of these drugs
    - Juvenile idiopathic (rheumatoid) arthritis
    - Plaque psoriasis and psoriatic arthritis (effects skin and joints)
    - Ankylosing spondylitis
  + **ETANERCEPT (*Enbrel*®, 1998)** 
    - Etanercept is a genetically engineered recombinant fusion protein that has the soluble form of the TNFα receptor (p75) attached to the Fc portion of human IgG1 and as a consequence forms dimeric agent that binds TNFα
    - ***ADMINISTRATION***
      * Etanercept is injected subcutaneously twice per week and inhibits the  action of TNFα by competing for soluble TNFα.
      * Used with or without methotrexate
  + **INFLIXIMAB (*Remicade*®, 1998)** 
    - Infliximab is a genetically engineered chimeric (man (Fc portion is human)-mouse) monoclonal antibody against TNFα. Binds soluble/free and membrane associated TNF.
    - ***INDICATIONS***
      * It is also been approved for the treatment of Moderate to severe Crohn’s disease and ulcerative colitis.
    - ***ADMINISTRATION***
      * IV infusions are administered every 8 weeks.
      * In RA, it is administered with methotrexate, which appears to limit the generation of antibodies against infliximab that otherwise reduce the benefits of subsequent treatments
  + **ADALIMUMAB (*Humira*®, 2002)**
    - Similar to infliximab except it is a human-human antibody against TNFα and administered more frequently
    - ***INDICATIONS***
      * RA, AS, psoriatic arthritis, psoriasis, and also Crohn’s Disease, and ulcerative colitis (IBD)
    - ***ADMINISTRATION***
      * SC injection, 1x per 2 weeks (t1⁄2 = 2 wks)
      * Used with or without methotrexate (MTX)
  + **CERTOLIZUMAB (*Cimzia*®, 2008)**
    - ******Anti-TNFα human Fab antibody fragment conjugated to pegol
    - ***ADMINISTRATION AND USE***
      * SC injection, 2x 200 mg per 4 weeks (t1⁄2 = 2 wks)—longer half life
      * Used with or without methotrexate (MTX)
      * Indicated for RA and Crohn’s Disease
  + **GOLIMUMAB (*Simponi*®, 2009)** 
    - ***MECHANISM***
      * Anti-TNFα human antibody
    - ***ADMINISTRATION AND USE***
      * SC injection, 1x per 4 weeks (t1⁄2 = 2 wks)
      * Used with methotrexate (MTX)
      * Indications RA, ankylosing spondolyitis, psoriatic arthritis
  + **TNF**α **BLOCKERS: WARNINGS AND ADVERSE EFFECTS**
    - ***IMMUNOSUPPRESSION (compare with use of glucocorticoids)***
      * Serious infections and sepsis seen - 0.04 per patient year - some fatal
        + Tuberculosis – 13 cases during clinical trials

Evaluate for active or latent TB before initiation of tx—because it can be reactivated if you suppress your immune system

* + - * + ↑ risk of Invasive opportunistic fungal infections – 6 cases
        + Upper respiratory tract infection 1 per patient yr
        + Initiation of treatment is contraindicated if patient has active infection or patient has recurrent infections
        + Live vaccines contraindicated with TNF blockers
      * Neurologic events
        + Rare cases of exacerbation of demyelinating diseases, e.g. multiple sclerosis
      * Malignancies in children - ***under investigation***
        + 30 cases in children/young adults 1998-2008

Incidence of lymphoma (~50%) (10/2468) higher than in general population – link to anti-TNFα therapy?

Immune system helps protect us from infection and also plays a role in preventing cancer in our bodies

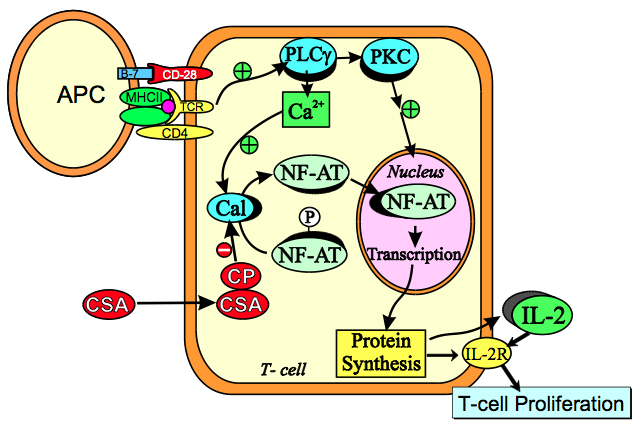
* + - * + FDA continues to receive reports of hepato-splenic T-cell lymphoma (HSTCL) most with IBD (4/14/2011)
      * Autoimmunity
        + ANA titers may increase during therapy

lupus-like syndrome possible

* + - * Antibodies against drug
        + Decreased by methotrexate, azathioprine, etc
* ***DRUGS THAT TARGET INTERLEUKINS***
  + **ANAKINRA (*Kineret*®, 2001)**
    - Recombinant, human IL-1 receptor antagonist (IL-1Ra), (a 153 amino acid protein), which binds to the IL-1 receptor and prevents IL-1 from binding.
      * ↓ IL-1 effects
    - ***USE*:** Treatment of Rheumatoid arthritis
      * For moderate-severe R. Arthritis if inadequate response to DMARDs,  + or – MTX, etc
      * **Not** to be used with TNF blockers, because both ↓ immune system functioning 🡪 increases frequency of infections
    - ***ADMINISTRATION***
      * **SC injection 1 per day** (half-life = 4-6 hours)
    - ***ADVERSE EFFECTS*:** ↑ risk ofinfections, (no live vaccines should be used), neutropenia, most common is injection site reaction
  + **TOCILIZUMAB (*Actemra*®, 2010)**
    - Humanized monoclonal antibody against soluble and membrane IL-6 receptors – blocks signaling, e.g. OCs
      * IL-6 has been shown to be important in activating osteoclasts which break down bone
    - ***INDICATIONS and ADMINISTRATION*** 
      * Adults: moderate -severe RA **not responsive to TNFα** antagonists
        + IV infusion every 4 weeks + or – MTX
      * Children > 2 y.o.
        + systemic juvenile idiopathic arthritis (SJIA) - IV infusion every 2 weeks
    - ***ADVERSE EFFECTS:*** 
      * Infections/malignancy
      * GI perforations in patients with diverticulitis
      * Hyperlipidemia
      * Symptoms of demyelination

**AGENTS *THAT* TARGET T-CELL *AND* INTERLEUKIN 2 (IL-2)**

* IL-1 is secreted by the APC and IL-2 is important in the maturation and division of proliferation of active T-cells
* USES
  + Suppression of immune and inflammatory response
    - Prevent rejection of transplants—more important for this
    - Autoimmune/inflammatory diseases
* ***AGENTS THAT TARGET T-CELLS***
  + Useful in suppression of immune and inflammatory response, preventing rejection of transplants and treating autoimmune/inflammatory diseases.
  + **CYCLOSPORINE (*Neoral*®, *Sandimmune*®, 1983)**
    - Cyclic hydrophobic (very) peptide produced by fungi🡪*Beauveria nivea*
      * Very high partition coefficient—high enough that our GI tract has trouble absorbing them—need to dissolve them in an ethanol mix to try and get some uniform absorption
    - ***USES***
      * Prevent rejection in renal, liver and heart transplants *VERY IMPORTANT*
      * Autoimmune diseases RA, IBD, myasthenia gravis
      * Can be used in conjunction with glucocorticoids (prednisone) and azathioprine (or could replace this w/ mycophenolate which has fewer side effects)
    - ***MECHANISM***



* + - * T-cells get activated by the APC (w/ second signal from B7 on APC and CD28 on T-cell 🡪 ↑ Ca). Signal transduction involves an increase in cytosol Ca2+, which activates **calcineurin** (Cal), a phosphatase that dephosphorylates NF-AT (nuclear factor of activated T-cells)—the phosphate normally hides the target sequence that can allow it to go into the nucleus. NF-AT can now enters the nucleus and turns on synthesis of cytokines such as interleukin-2 and its receptor, which induces T-cell proliferation. **Cyclosporine binds to a cyclophilin (CP) and inhibits calcineurin, thus inhibiting T-cell activation/proliferation**
        + so blocks formation and activity of IL-2
    - ***PHARMACOKINETICS***
      * ***ADMINISTRATION***
        + Due to insolubility in water, it is usually administered orally as solution in an ethanol/corn oil/castor oil derivative mix in capsules or diluted into orange or apple juice to produce a “microemulsion”

Gut🡪 liver where it is a substrate for the P450 system oxidation and also a substrate for P-gp so this can ↓ absorption by kicking it back into the gut and into the bile

* + - * + Variable absorption 20-50% -*Neoral*® > *Sandimmune*®
        + 1st pass metabolism significant - metabolized by **CYP3A4** and  substrate for **P-gp** (kicks hydrophobic things out of cells)

it is a hydrophibic substance so its not surprising that its metabolized by P450 system

* + - * + Many drug interactions
        + Significant toxic effects

Assay levels in the blood to make sure patient is getting the right dose

* + - * + IV: only if oral administration not possible
      * ***RESULT***: Need to assay blood levels to establish appropriate dose
    - ***TOXICITY*** 
      * **Nephrotoxicity most common and important** (20-38% in allografts). Difficult to distinguish from kidney rejection in kidney transplant patients
      * Others
        + Hypertension

50% of patients w/ kidney transplant

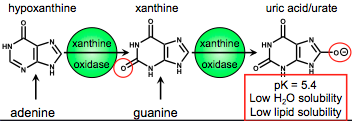
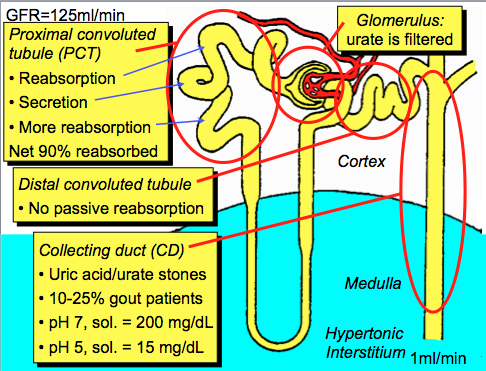
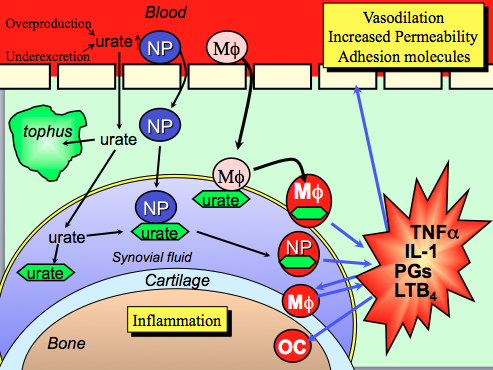
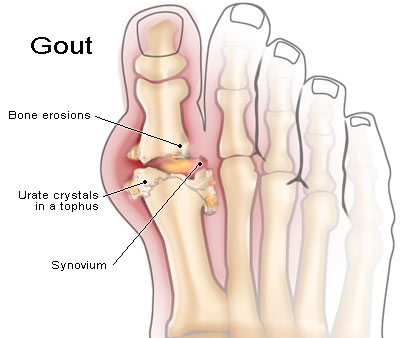
100% of patients w/ heart transplant

* + - * + Hirsutism
      * Little effect on bone marrow
        + Mant of the cytotoxic drugs (like azathioprine) do have toxic effects on bone marrow so you don't really want 2 drugs with same side effects b/c it ↑ the likelihood of them occurring
    - ***DRUG INTERACTIONS - IMPORTANT –*b/c narrow therapeutic window** 
      * Drugs that inhibit CYP3A4 or P-glycoprotein may **potentiate toxicity** 
        + ketoconazole, itraconazole, (antifungals)
        + erythromycin, clarithromycin, grapefruit juice (esp in GI tract), etc.
        + Ritonavir is most efficacious inhibitor of CYP3A4
        + Cyclosporin itself inhibits CYP3A4
      * Drugs that induce the CYP3A4 or P-gp may lead to **organ rejection** b/c will be metabolized faster and level of drug in the body will ↓
        + Phenobarbital - CNS depressant
        + Carbamazepine - anticonvulsant
        + Phenytoin-anticonvulsant
        + Rifampin - antimicrobial used for tx Tb
        + **St. John’s Wort** - dietary supplement - “antidepressant”
      * Other nephrotoxic drugs
        + e.g. amphotericin B, aminoglycosides, NSAIDs etc
      * Cyclosporine can inhibit metabolism of drugs by blocking CYP 3A4
        + E.g. lovastatin – increases risk of rhabdomyolysis
  + **TACROLIMUS (FK506, *Prograf*®, 1994)**
    - Another hydrophobic cyclic compound produced by fungi that inhibits calcineurin—it is very similar to cyclosporin
      * Properties **very similar to cyclosporine**, ***BUT*** has different receptor - “FK binding protein” (FKBP25) 🡪 inhibition of IL-2 production and IL-2 receptor production
      * Approved for heart, liver and kidney transplants to ↓ rejection
      * Used topically for treating eczema
  + **SIROLIMUS (*Rapamune*®, 1999)**
    - Another hydrophobic cyclic compound, related to tacrolimus produced by another fungi, ***BUT* different mechanism and little nephrotoxicity, hence it is used synergistically with cyclosporine and prednisone.**
    - ***MECHANISM*** 
      * Binds to a “FK binding protein”, FKBP12, but unlike cyclosporine and tacrolimus it does ***NOT*** block calcineurin or IL-2 production
        + It acts at a later step
      * Block a kinase “mTOR” – a kinase involved in cell cycle
        + mTOR= Mammalian Target Of Rapamycin—this is a receptor
      * Blocks T-cell proliferation induced by cytokines
      * Blocks B-cell proliferation and differentiation into Ig producing cells
      * Blocker proliferation of endothelial and SM cells –so also used for coating stents
    - ***USE*** 
      * Prophylaxis of renal transplant rejection
      * Is used in combination with cyclosporine and corticosteroids –they act at different steps in the pathway
      * Not for liver transplant - hepatic artery thrombosis risk
    - ***SIDE EFFECTS*** 
      * Little nephrotoxicity alone, **But**, sirolimus aggravates CSA (cyclosporine)-induced renal dysfunction (makes CSA nephrotoxicity worse!)
      * Triglycerides and cholesterol increase (51%, 44%) and further increased by concomitant use of CSA (cyclosporin A= cyclosporine)
        + All patients should be monitored for hyperlipidemia
        + 50% patients will need treatment
        + When risk is minimal—use both drugs together and then once there is a ↓ chance of rejection wean the patient off the CSA and continue treatment w/ Sirolimus
      * Increased BP
      * Thrombocytopenia (37%) –blocks proliferation of a lot of cells
    - ***DRUG INTERACTIONS -*** 
      * Bioavailability is only 14% and metabolized via CYP 3A4, hence susceptible to drug interactions, e.g. cyclosporine (CSA inhibits its metabolism so levels of it will ↑ in the blood)
      * In addition to CSA, many drug interactions possible
        + Sirolimus normally administered 4 hr after CSA

Don't administer simultaneously

* + - * Monitoring may be necessary
    - ***ADMINISTRATION***
      * Not soluble in water must be dissolved in an oil base
      * Administered mixed with water or orange juice, **NOT grapefruit**
  + **ABATACEPT (*Orencia*®, 2005)**
    - Normal physiology
      * To prevent over proliferation of T cells the T cell has a soluble receptor for B7 which binds to B7 (binds a lot more strongly to B7 than CD28 does!) so this is produced by the proliferating T cells and will eventually turn off T cell proliferation
        + If you knock this out the animal dies—it's a lethal mutation
    - CTLA4 soluble B7 receptor attached to Fc of IgG1
      * ABATACEPT is a Recombinant form of this soluble B7 receptors attached to an antibody
    - CTLA4 is a natural B7 antagonist binds 20x more strongly than CD28.
    - ***ACTION***  Inhibits T-cell proliferation
    - ***INDICATION***
      * Rheumatoid arthritis if inadequate response to MTX or TNFα antagonists
        + Should not be used with TNFα antagonists (infliximab, etc)
      * Not recommended for use with anakinra (IL-1 inhibiting drug)
  + **DACLIZUMAB (*Zenapax*®, 1997) and BASILIXIMAB (*Simulect*®, 1998)**
    - Drugs for prophylaxis of acute rejection of renal transplants
    - ***MECHANISM*** 
      * Chimeric mouse/human monoclonal antibodies against IL-2 receptor on activated T-cells
        + Antibodies against the IL-2 receptor
    - ***INDICATION***:
      * Prevention of rejection of renal transplants used with CSA and corticosteroids
        + These are used SHORT TERM (days or weeks after surgery)
    - ***ADMINISTRATION (IV)***
      * Daclizumab before surgery and 4 doses at 2 wk intervals
      * Basiliximab 2 hr before surgery and 4 days after transplantation

**DRUGS FOR GOUT**

* **PATHOGENESIS *of* GOUT**
  + ***What is gout?***A disease that results from hyperuricemia
  + ***What is “hyperuricemia”?***– Too much uric acid in the blood
  + ***What is uric acid?*** It is a waste product from the breakdown of purines (Adenine and guanine)
* **URIC ACID** 
  + Uric acid is product of oxidation of purine bases from *de novo* synthesis, tissue DNA, and diet
  + Normally, 600-800 mg/day produced/excreted
  + Normal plasma urate 6.8 mg/dL men, 6 women
  + Risk of gout if plasma urate > 7 mg/dL
    - More common in men than women
  + ***ELIMINATION of URIC ACID***
    - Has low water and lipid solubility
      * Solubility of uric acid is low the lower the pH and most peoples urine tends to be on the acidic side—which makes this problem worse
    - 25-33% eliminated in GI tract - metabolized by bacteria in the colon
    - Rest is eliminated by kidney (300-600 mg/day)
      * Uric acid get filtered at the glomerulus (GFR= 125 ml/min) and as we get further along in the renal tubules we reabsorb stuff and get the volume down to 1 ml/min which will result in very concentrated uric acid. Uric acid is not soluble so it will ppt and clog up the kidneys🡪 renal failure. BUT 90% of it gets reabsorbed
      * Filtration rate = GFR, but only 10% filtrate is excreted
        + Why? Active reabsorption occurs in proximal tubule
    - Significant amounts are secreted by pumps in PT
    - Second active absorption site
    - There is very little passive non-ionic reabsorption
    - If amount in urine exceeds solubility, uric acid crystals/stones form in CD - ***nephrolithiasis***
* **HYPERURICEMIA**:
  + CAUSED BY
    - Increased production of uric acid
    - Decreased excretion of uric acid
    - Or Combination of both
  + **PRIMARY GOUT**
    - More common in men (10x), genetic links
    - Risk increases with age, body weight, alcohol, diet
  + **SECONDARY GOUT**
    - Drug induced, e.g. diuretics
      * Thiazide diuretics especially—they compete with uric acid for secretion into the tubule—so ↓ amount that get into the kidney and leading to ↑ levels in the blood
    - Chemotherapy of cancer kills cells 🡪 big influx of DNA (purines) 🡪 ↑ purine metabolism🡪 ↑ uric acid
  + **CONSEQUENCES**
    - **ACUTE GOUTY ARTHRITIS** 
      * Uric acid enters the synovial fluid of the joints where the pH tends to be acidic. Uric acid forms Crystals of Na urate in joint and cause inflammatory cells (macrophages, etc) to come in an try and eliminate these crystals and this activates macrophages which release TNFα, IL-1, PG’s, LTB4, etc.
      * Often affects big toe (metatarsophalangeal joint)
        + 
        + WHY? thought to be because they are a little bit cooler and the ↓ temperature ↑ likelihood that these crystals will form
      * Attacks often begin during night with extreme pain
        + Last hours–days if not treated
        + Occurrence at night is thought to be because you’ve been standing on your foot all day long and the ↑ pressure of the joints 🡪 influx of more synovial fluid 🡪 ↑ risk of uric acid getting into the joints 🡪 at night we lie down and that pressure and fluid starts to dissipate back into the blood and the uric acid gets concentrated and triggers an attack
      * May progress to chronic **nonsymmetric synovitis** (kind of like rheumatoid arthritis)
      * 
        + Hyperalgesia!!! Often begins in the night

PG’s produce hyperalgesia!!

* + - **TOPHACEOUS GOUT** – late complication
      * After prolonged hyperuricemia, ***tophi*** - large gritty deposits of uric acid crystals - form in connective tissue, tendons, SC
      * Tophi can damage joint and neighboring soft tissues, e.g. nerve compression → carpal tunnel syndrome
      *   
    - **NEPHROLITHIASIS** (10-25% patients)
      * Especially if urine concentrated—so drink a lot of water to ↓ concentration
      * Especially if urine has low pH—Na-bicarbonate to ↑ pH of urine (take an antacid)
      * Especially if renal excretion exceeds 1100 mg/day
    - **GOUTY NEPHROPATHY**
      * **Acute renal failure** due to obstruction of collecting ducts or ureters due to massive precipitation of uric acid crystals, can occur after initiation of chemotherapy
      * **Chronic nephropathy** due to Na urate crystals deposited in renal parenchyma → inflammation
* **DIAGNOSIS of MSU GOUT**
  + Extracellular and intracellular monosodium urate (MSU) crystals, as seen in a fresh preparation of synovial fluid, illustrate ***needle- and rod-shaped strongly negative birefringent crystals*** (compensated polarized light microscopy; 400×).

**TREATMENT OF GOUT **

* Two approaches
  + Treat inflammation of acute gouty arthritis
  + Treat hyperuricemia/chronic disease
* **ANTIINFLAMMATORY DRUGS**
  + Treatment of acute gouty arthritis
    - Colchicine
    - NSAIDs
    - Glucocorticoids
    - \*\*Short duration therapy
  + **COLCHICINE**
    - An alkaloid found in the dried seeds of the autumn crocus—a flower, *Colchicum autumnale* (Extracts used for joint pain since 6th century, and for gout since 1763, 1820)
    - Extracts used for joint pain since 6th century, and for gout since 1763, isolated in 1820.
    - First approved for monotherapy July 30, 2009
    - Also approved for familial Mediterranean fever
    - ***MECHANISM***
      * Binds to tubulin (which makes the spindles during cell division) causing dissociation of microtubules (which help move chromosomes during cell division!)
      * Blocks cell division, motility of cells (recruitment), phagocytosis in neutrophils & macrophages
        + May block macrophage uptake of the crystals 🡪 ↓ inflammatory response
    - ***ADMINISTRATION* –** oral
    - ***TOXICITY - IMPORTANT***
      * Blocks cell division in GI tract, bone marrow
        + Produces nausea, vomiting, diarrhea, abdominal pain
        + They say to ↑ dose until you vomit and that's the max dose you can use
      * Overdose can be lethal, especially when > 4 mg/day given IV, and in 2008 FDA removed IV formulations from market, never had actually received approval
    - ***USES***
      * **Treatment of ACUTE attack** – “**High dose”**
        + Pain, swelling, redness usually gone in 48-72 hrs
        + Maximum total dose limited to avoid serious toxicity
        + **First formulation approved by FDA in 2009!** (*Colcrys*®, 2009)

Standard dosing lowered based on new study data

Oral 1.2 mg, then 0.6 mg at 1 hour

**Maximum total dose**: 1.8 mg over 1 hr

Higher /additional doses provide no additional relief

* + - * **NSAIDs** usually preferred as **fewer side effects**
      * **PROPHYLAXIS of acute gouty arthritiS** “**Low dose”**
        + Useful in combination with hypouricemic drugs
        + Discontinue if symptom free for 1 year
        + **Dosing approved by FDA** (*Colcrys*®, 2009)

0.6 mg 1x or 2x per day

**Maximum dose** 1.2 mg per day

* + - ***DRUG INTERACTIONS***
      * Drug interactions with CYP3A4 and P-gp inhibitors
        + Cases of fatal toxicity have resulted
  + **INDOMETHACIN**
    - A potent NSAID for short term therapy
    - Drug of choice, if NSAIDs not contraindicated
      * Ibuprofen, diclofenac, etc. also effective
    - As effective as colchicine for an acute attack of gout
      * 75 mg, *then* 50 mg/6hrs for 2 days, *then* 50 mg/8hrs for 1–2 days
    - If response inadequate, use a glucocorticoid

***HYPO*URICEMIC DRUGS**

* Goal to keep plasma urate < 5 mg/dL
  + To prevent acute attacks
  + To eliminate tophaceous deposits
  + \*\*Long-term (life-long) therapy often needed
* **URICOSURIC AGENTS**
  + Drugs that *increase* urinary excretion of uric acid--↓ levels in the blood
    - **PROBENECID**
    - **SULFINPYRAZONE**
  + Especially useful in patients who excrete *less than* 600 mg/day i.e. **when problem is *lower than normal* excretion of uric acid**
    - We have renal problems if we have too much uric acid in the urine—so if you already have a patient who has too much you don't want to use these drugs
  + **PROBENECID**
    - Renal handling
      * 90% of this drug is bound to albumin, so most is actively secreted into tubule
        + we saw this before used to ↓ the secretion of penicillin in order to ↑ it’s half life
      * Undergoes almost complete non-ionic reabsorption
      * Plasma t½ = 5-8 hrs
        + Because as it gets concentrated down the tubule it has a reasonable half life and its gets reabsorbed
    - ***ACTIONS***
      * **Low doses** block anion secretion in kidney, etc.
        + So at low doses you actually block the secretion of uric acid from the blood into the kidney and we don't want this!
        + Developed to inhibit elimination of penicillin
      * **Higher doses** specifically **block urate reabsorption by acting from the inside of the tubule**
        + 90% of uric acid is reabsorbed in the PCT of the kidney
        + This is what we want!
        + **Net effect: increased excretion of urate**
    - ***USAGE***
      * 1-2 g administered per day
    - ***CONSEQUENCES OF THERAPY***
      * **Increased excretion of urate increases the risk of uric acid kidney stones**
        + To prevent this

Consume 1500 ml water per day to dilute the urine, and…

Administer 3-7.5 g Na HCO3 per day to alkalinize urine until plasma urate is normal ***and*** tophi have disappeared

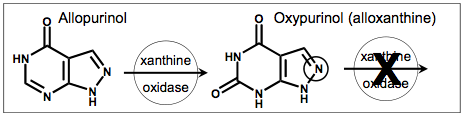
* + - * + DO NOT USE if there is *overproduction* of uric acid
      * **Acute gouty arthritis attacks can be precipitated** 
        + **DO NOT** initiate treatment until acute attack subsided

When you use this drug, and you are mobilizing those tophi, the risk of an acute attack goes ↑--maybe because the tophi around the joints start to dissolve and the uric acid goes into the joint and ppt an acute attack

* + - * + Combine with ***low dose*** colchicine, e.g. *Col-probenecid*®

To promote uric acid excretion

* + **SULFINPYRAZONE—NO LONGER ON THE MARKER ANYMORE** 
    - Strong organic acid, pK 2.8
    - Uricosuric action similar to probenecid
    - Only other uricosuric drug approved in USA, but marketing discontinued
  + **SALICYLATES: *Review***
    - Low doses inhibit urate secretion via renal anion pumps—so low doses will elevate blood levels of uric acid
    - High doses will also inhibit urate reabsorption in proximal tubule – “uricosuric action”
    - ***DRUG INTERACTIONS***
      * Since salicylates block the renal anion pumps, **all doses block entry of probenecid into tubule**
        + **Compete w/ probenecid for transport**
      * **Salicylates** therefore inhibit uricosuric action of probenecid and are therefore **contraindicated**
* **DRUGS that INHIBIT URIC ACID SYNTHESIS**
  + Decrease uric acid *production,* therefore *decrease* urinary excretion of uric acid
    - **ALLOPURINOL**
    - **FEBUXOSTAT**
  + Especially useful in gout patients that *produce too much* uric acid, *excrete >800 mg/d* or have a history of renal stones or renal disease
  + **ALLOPURINOL (*Zyloprim*®, 1966)**



* + - ***MECHANISM AND PHARMACOKINETICS***
      * Allopurinol looks like a purine
      * Allopurinol is a competitive inhibitor/substrate of XO
      * Allopurinol is oxidized to **oxypurinol** by XO
        + Result: Allopurinol short t½ = 1-2 hr
      * **Oxypurinol is a potent non-competitive inhibitor of XO**
      * Like uric acid, oxypurinol is filtered and reabsorbed
        + Result: long t½ = 18-30 hr, long duration of action
    - ***CONSEQUENCES of THERAPY***
      * **Plasma urate ↓**; hypoxanthine↑; xanthine↑ (b/c your blocking their metabolism by XO)
        + Urate in tophi begins to dissolve
        + More hypoxanthine and xanthine recycled to purines
      * **Urine urate ↓**; hypoxanthine↑; xanthine↑ (b/c your blocking their metabolism by XO)
        + Prevents formation of uric acid kidney stones, prevents nephropathy
        + Although hypoxanthine and xanthine solubility is low, concentration in plasma and urine rarely exceed solubility

These two things are more soluble than uric acid and usually you don't have problems with these but you will still want to maintain ↑ levels of fluids to dilute the urine

* + - * + ***However;*** to ensure xanthine stones (calculi) **do not** form, urinary output should be maintained at 2L per day and at a neutral or preferably slightly alkaline pH
      * Incidence of acute gouty arthritis attacks **may actually increase** during first months of therapy
        + **DO NOT** begin therapy during an **acute attack** b/c it will make things worse and

Begin therapy with low dose, 100 mg/day, increase weekly until plasma urate <= 6 mg/dL or dose of 800 mg reached

* + - * + **Use colchicine** (and/or NSAID) until serum uric acid is normal and no attacks for several (3) months, or tophi gone

Attacks decline after tissue stores are reduced—don't need colchicine after this

* + - ***ADVERSE REACTIONS***
      * **Most serious,** rare but can be **fatal:** Skin rash/fever → i.e. necrolysis, vasculitis, hepatitis, renal failure
    - ***DRUG INTERACTIONS***
      * Azathioprine and mercaptopurine (MP)
        + MP is metabolized to thiouric acid by xanthine oxidase so if you use allopurinol the levels of MP in the blood go way up
        + Administration of allopurinol requires dose↓ to 25-33%
      * Probenecid and other uricosurics
        + Inhibit reabsorption of oxypurinol and decrease its half-life
    - ***INDICATIONS***
      * Patients with **signs and symptoms** of gout, ***not recommended*** for **asymptomatic** hyperuricemia
      * Patients with leukemia, lymphoma and malignancies receiving chemotherapy 🡪 ↑ purine metabolism that elevates urate
  + **FEBUXOSTAT (*Uloric*®, 2009)**
    - ***MECHANISM***
      * Xanthine oxidase inhibitor
    - ***DRUG INTERACTIONS***:
      * drugs metabolized by XO
        + Azathioprine *-contraindicated*
        + Mercaptopurine *-contraindicated*
        + Theophylline (1,3-di-Me-xanthine) Cmax↑ 6%; AUC↑ 6.5%, but 1-Me-xanthine in urine↑ x400
* **DRUGS/ENZYMES that METABOLIZE URIC ACID**
  + Uricase metabolizes urate to soluble allantoin
    - Humans don't have this but some animals do !
  + Decrease uricemia and therefore decrease excretion of uric acid
    - **RASBURICASE** (*Elitek*®) and **PEGLOTICASE** (*Krystexxa*®)
  + **RASBURICASE (*Elitek*®, 2002)**
    - Uricase from the fungus *Aspergillus flavus –* recombinant form from yeast
    - ***INDICATION***:
      * Pediatric patients with leukemia, lymphoma, and solid tumors undergoing chemotherapy expected to elevate plasma uric acid b/c ↑ purine metabolism due to ↑ cell death
    - ***ADMINISTRATION***
      * Infused over 30 min 1x per day for 5 days starting 4-24 hr before chemotherapy
    - ***ADVERSE EFFECTS***
      * Anaphylaxis
  + **PEGLOTICASE (*Krystexxa®,* 9/2010)**
    - Mammalian URICASE conjugated to PEG (polyethylene glycol)—PEG makes them bigger and protects them from breakdown which prolongs the half life.
    - ***INDICATION***:
      * Treatment of gout in adults refractory to XO inhibitors
    - ***ADMINISTRATION***:
      * IV infusion every 2 weeks
    - ***ADVERSE EFFECTS***
      * Severe allergic reaction in 25% patients, anaphylaxis in 6.5% patients
      * Need preinfusion of antihistamines and glucocorticoids

**DRUGS FOR SKIN DISORDERS**

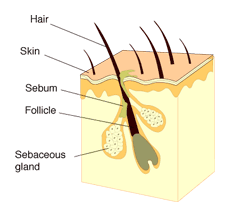
**PSORIASIS AND ACNE**

* **PSORIASIS**
  + ***What does it look like?***
    - 
    - Normal turnover time of keratinocytes is 1 month, in psoriasis, it is decreased to 3-4 days
      * Rapid growth driven by activated T-cells (IL-17) in skin
        + CSA tx in patients with this showed to ↓ their symptoms and that's how they figured out T-cells were driving this whole process.
      * Keratinocytes, Fibroblasts, → cytokines to recruit inflammatory cells
  + **PSORIASIS**
    - Chronic inflammatory, T-cell/immune-mediated disorder with hyperproliferation of keratinocytes
      * Skin becomes thick and red - blood vessels dilated
      * “*Plaque psoriasis*” most common variety (80%)
        + Affects elbows, knees, trunk, scalp, feet, hands and nails
        + Dead cells accumulate, produce white flaky patches
      * “*Inverse psoriasis*” affects intertriginous regions, e.g.
        + armpits, groin, gluteal cleft, submammary region and navel
      * *“Psoriatic arthritis”* develops in 5-10% patients
    - About 5.5 million (1-2%) in USA, often seen between 15-35 y/o, but can occur at any age
      * 50% have family history of psoriasis
  + **PSORIASIS THERAPY**
    - *Mild psoriasis* < 2% skin - topical therapy
      * Topical glucocorticoids – *most common initial tx*
      * “Vitamin D”: Calcipotriene
      * Keratolytic drugs: salicylic acid, sulfur
    - *Moderate* *psoriasis* 3-10% - topical therapy
      * Coal tar, anthralin with or without UV-B, retinoids
    - *Moderate-Severe* *psoriasis* - systemic therapy
      * Phototherapy *plus* systemic photosensitizer
      * Methotrexate, acitretin
      * **ALEFACEPT, EFALIZUMAB, CYCLOSPORINE**
    - **OTHER DRUGS for PSORIASIS** 
      * **ETANERCEPT (*Enbrel*®), INFLIXIMAB (*Remicade®*) and ADALIMUMAB (*Humira*®)**
        + Agents that target TNFα

RA drugs, now also approved for psoriasis

* + - * + ***INDICATIONS for PSORIASIS***

Chronic moderate to severe plaque psoriasis in adult patients (18 years or older), who are candidates for systemic therapy or phototherapy.

**Psoriatic** **arthritis**

* **ACNE**
  + A disease of the pilosebaceous unit
    - ***Propionibacterium acnes***
    - Androgens → sebum (accumulates and stretches out the follicle producing a white head and black head)
    - Keratin
  + ***MOST COMMON DERMATOLOGIC DISEASE***
    - *Over 17 million affected in USA, 80% are between 11-30 y.o., more common in males*
  + ***PATHOGENIC FACTORS***
    - ***Androgens*** *promote development of sebaceous glands and sebum production in follicles in face, neck, shoulders, and back*
    - *Keratinization of epithelial cells lining follicle*
    - ***Result: Sebum*** *and* ***keratin*** *plug and expand pores*
    - ***Propionibacterium acnes*** *-an anaerobic bacterium -infection promotes inflammation*
  + *Mild cases: open comedos (blackheads)*
  + *Moderate cases: closed comedos (whiteheads)*
  + *Severe cases: closed comedos rupture into dermis → inflammation, abscesses and cysts develop*

**RETINOIDS/VITAMIN A**

* ***WHAT ARE RETINOIDS***
  + Retinoids are hormones that bind to intracellular retinoic acid receptors ***RAR* (α , β , and γ)** that are in the same super-family as corticosteroid and thyroxine receptors and also receptors designated RXR. RXR (is a coreceptor with all the other receptors mentioned) receptors enhance the activity of RARs, thyroid receptors, steroid receptors and calcitriol (vitamin D) receptors, and PPARs. Note that, unlike most hormones, retinoids are not synthesized in the body, but are derived from retinol (vitamin A) and β -carotene (provitamin A).
    - These receptors are all regulators of transcription and protein synthesis
    - β -carotene and all-trans-retinol. In the digestive tract a certain percentage of β- carotene is cleaved to produce retinol. Esters of retinol are stored in the liver. Various cis-isomers are produced in the body, although the all-trans form is the most potent. Oxidation of the alcohol to the aldehyde produces **retinal** (important for vision) and oxidation of this to the acid produces retinoic acid (most of its effects are from this form—acts like a hormone), which is 10-100-fold more potent than retinol and is the active form of vitamin A is all tissues except the retina.
    - β-carotene is orange stuff that makes tomatoes and carrots the color they are (due to absorption of light)
    - We don't make retinol or β-carotene in the body so we must get them from the diet
      * These are converted into hormones (retinoic acids)
        + Retinoic acid is a hormone, lipid soluble and spends most of its time bound to proteins (retinoic acid binding protein in the blood and the cells🡪CRABP)
* ***FUNCTIONS OF RETINOIDS***
  + Retinoids have a large number of important functions in the body. Two of the most important are those in the visual cycle and in the regulation of epithelial structure and function.
  + **VISUAL CYCLE**
    - 11-cis-retinal is the prosthetic group/agonist of rhodopsin, which is the primary receptor for light in both rods and cones and is in the same family as the G- protein-linked receptors.
      * The visual cycle involves conversion of **11-cis retinal to all- trans retinal**. Vitamin A deficiency leads to “night blindness”, often the first indication of deficiency.
  + **EPITHELIAL STRUCTURE AND FUNCTION**
    - Retinoic acid promotes generation of goblet cells and mucus production
    - Retinoic acid inhibits keratinization of the epithelium.
    - ***VITAMIN A DEFICIENCY***
      * Mucous cells disappear and epithelium becomes stratified and keratinized, e.g.
        + In lungs—the epithelium because keratinized so ↓ mucous that help clear out the lung🡪 this leads to irritation and infection
        + In cornea, the dryness and severe keratinization -*xerophthalmia* -leads to blindness
    - ***HYPERVITAMINOSIS***
      * Effects depend on age, dose and duration of therapy.
      * Fatal poisoning has occurred following ingestion of polar bear liver, which contains up to 12 mg retinol/g.
  + **RETINOL VERSUS RETINOIC ACID**
    - Retinol is absorbed from GI tract via a specific transport process and is bound in cells by a *cellular retinol binding protein* (CRBP). It is stored in liver as an ester. In the blood, retinol is transported by a *retinol binding protein* (RBP), which is secreted by the liver. In target tissues, it is bound to CRBPs prior to conversion the active species. In tissues other than the retina, retinol is oxidized to retinoic acid and bound to a *cellular retinoic acid binding protein* (CRABP).
    - Retinoic acid does not itself have a specific transport system in the gut and is transported in the plasma bound to albumin.
* ***RETINOIDS AS DRUGS***
  + Because of their effect on the structure and function of epithelia, retinoids are used for treating a number of skin disorders including acne, and psoriasis.
  + Acne is the most common skin disorder in the USA. This involves plugging of the hair follicle with sebum and keratin, which supports growth of *Propionibacterium acnes* which releases inflammatory fatty acids from the sebum, and inflammation. Lesions occur as comedones, papules, pustules, nodules and cysts. All except open comedones (black heads) are pre-inflammatory or inflammatory.
  + Three generations of drugs are available.
  + **RETINOL AND RETINOIC ACIDS**
    - These are identical to the natural physiological agents.
    - **TRETINOIN** *(Retin-A®,* 1971; *Renova®, 1995)*
      * Topical application for treatment of acne
      * In acne treatment, *Retin-A*® is comedolytic and inhibits keratinization - promotes expulsion of open comedones (promotes expulsion of sebum from the follicle)
        + Decreases cohesiveness of epithelial cells in follicle
        + Decreases thickness of *stratum corneum*
      * Other Effects – diminishes fine lines and wrinkles (*Renova*®)
        + Promotes dermal collagen synthesis

Glucocorticoids tend to ↓ collagen synthesis

* + - * + Promotes new blood vessel formation
        + Promotes thickening of epidermis
      * ***ADVERSE EFFECTS***
        + No systemic effects as only 10% is absorbed into circulation
        + Increases susceptibility to sunburn, use sunscreen (15SPF) and protective clothing
        + Not usually prescribed to pregnant patients (see below)
    - **ISOTRETINOIN** *(Accutane®, 1982)*
      * Systemic/oral therapy reserved for treatment of severe nodular acne in patients who are unresponsive to conventional therapy, including systemic antibiotics
        + very effective treatment
      * ***MECHANISM:***
        + Decreases sebum production
        + Decreases sebaceous gland size
        + Decreases keratinization
        + Decreases inflammation
      * ***SIDE EFFECTS***
        + Similar to those of hypervitaminosis A
        + **SIDE EFFECTS ON EPITHELIA**

Dryness of skin and mucous membranes - results in

Most common:

Dry itchy eyes, nose, mouth

Nose bleeds

Inflammation of lips (cheilitis)

Hair loss, peeling of skin from palms and soles when we have excess amounts

Sensitivity to UV light, use protection against sun

Inflammatory bowel disease—probably due to maintenance of normal epithelium in the gut

* + - * + **HYPERLIPIDEMIA** – 25%

Elevation of tri-glyceride levels

Sometimes increase in cholesterol (LDL) and decrease in HDLs - needs to be monitored

* + - * + **EFFECTS ON BONE FORMATION**

Long-term therapy- calcification of ligaments and tendons surrounding joint

Decreased bone mineral density

Pain in joints muscles

* + - * + **SUDDEN REDUCTION IN NIGHT VISION**

Seems paradoxical—not enough vit A can go blind and if you have too much you can loose your ability to see at night at least temporarily

* + - * + **PSEUDOTUMOR CEREBRI**- RARE

Benign cerebral hypertension, can be mistaken for a tumor

Might have headaches

This HTN can leads to edema of optic disk (papilledema), which can lead to permanent blindness

More likely if tetracycline co-administered

* + - * + **DEPRESSION** - RARE, BUT...

Depression and suicidal ideation may be associated with retinoids. Since 1989, 12 patients have committed suicide

Must be discussed with patient, so that any signs or symptoms are reported to physician and therapy stopped

* + - * **CONTRAINDICATION**: **PREGNANCY**
        + Isotretinoin is a pregnancy category X drug and should not be taken during pregnancy. There is a very high risk of birth defects, e.g.

Skull abnormalities

External ear malformation

Facial malformation

Cleft palate

CNS abnormalities

CV abnormalities

* + - * + ***IMPORTANT: To prevent birth defects isotretinoin must be prescribed under the iPLEDGE program, which was introduced march 1, 2006 and replaced the S.M.A.R.T.***

*LOTS OF THINGS have to be done to make sure the woman is aware of the side effects and is not at risk of becoming pregnant*

* + **ACITRETIN AND ETRETINATE - SYNTHETIC ANALOGS**
    - These contain an aromatic ring, but retain the flexible side chain and therefore interact with most RARs. They are approved for systemic treatment of psoriasis. Their side effects and contraindications are similar to isotretinoin.
      * **ACITRETIN** (*Soriatane*®, 1996) is the active metabolite of etretinate (*Tegison*®, 1986-2003). Etretinate accumulates in adipose tissue and has a very long half-life (120 days) compared with acitretin (49 hours). Because this increases risk of birth defects etretinate has been removed from market (2003).
      * However, if ethanol is consumed by patients taking acitretin, etretinate is synthesized, consequently, alcohol should be avoided during therapy up to 2 months after the last dose.
      * Also, patients should not become pregnant for at least 3 years after the last dose
      * Also patients should not donate blood during therapy or for 3 years after therapy
      * **MECHANISM in PSORIASIS:** 
        + Inhibits proliferation of epithelial cells
        + Inhibits keratinization of epithelial cells
        + Inhibits differentiation of epithelial cells
  + **TAZAROTENE (*Tazorac*®, 2000; *Avage*®, 2002)**
    - Tazarotene is a synthetic retinoid with an aromatic ring in the side chain, which restricts the flexibility of the structure. Thus, although it binds to all three retinoic acid receptors RARα, β , and γ, it has some selectivity for β and γ.
    - It is a prodrug, which is hydrolyzed to produce a carboxylic acid – tazarotenic acid – the active drug. It is used topically for the treatment of both acne and psoriasis and wrinkles. First topical retinoid approved for psoriasis
    - *Avage*® is the same preparation approved for (-quote from drug label-) “mitigation of facial fine wrinkling, facial mottled hyper- and hypo-pigmentation, and benign facial lentigines in patients who use comprehensive skin care and sunlight avoidance programs”...it “DOES NOT ELIMINATE or PREVENT WRINKLES, REPAIR SUN-DAMAGED SKIN, REVERSE PHOTOAGING, or RESTORE MORE YOUTHFUL OR YOUNGER SKIN.” In one study, after 24 weeks treatment 16% of patients treated with vehicle had improvement, while 40% treated with tazarotene had improvement.
      * Use is contraindicated in women who are or may become pregnant
      * Most common side effects are limited to the skin
        + Peeling, red skin, dry skin, burning, itching
        + Avoid exposure to sun, or UV lamps
  + **BEXAROTENE (*Targretin*®, 1999)**
    - Bexarotene is a drug that is a selective agonist for retinoid X receptors (α, β, γ), and does not activate RAR receptors.
    - ***EFFECTS***
      * Inhibits growth of tumor cell lines of hematopoietic and squamous cell origin
    - ***INDICATION***
      * Treatment of cutaneous manifestations of cutaneous T-cell lymphoma (CTCL) in patients resistant to one prior systemic therapy
    - ***CONTRAINDICATED*** in pregnancy – precautions similar to isotretinoin
    - ***SIDE EFFECTS*** 
      * Elevation of TGs, LDL cholesterol
      * Hypothyroidism

**REGULATION, DEVELOPMENT AND SELLING OF DRUGS**

* To prescribe drugs responsibly requires some understanding of the processes of drug development and marketing, and the roles and interests of industry, government, organized medicine, and individual physicians in these processes.
* Drugs are available as prescription and non-prescription (over-the-counter, OTC) drugs. Human use, regulation of the sale and distribution of the drug, content of the package insert, and the content of marketing and “educational” materials for both medical professionals and for the public all must receive approval. That is the role of the U.S. Food and Drug Administration.
* **DRUG DISCOVERY AND DEVELOPMENT**
  + Potentially useful drugs are identified by (a) chemical modification of a known drug, (b) screening of synthetic and natural products for desirable effects; and (c) design of new drugs based on advances in biology and in the understanding of the nature of the disease. Very few of these reach the stage of human trials, and even fewer become marketed drugs. Almost all of this work is performed by, or supported by the pharmaceutical industry.
  + These chemicals are screened by a variety of in vitro and in vivo methods to detect biological activity (both potentially beneficial and adverse). At some point in this process, a patent is obtained. This protects the patent holder and provides exclusive rights to market the drug, but also starts the clock for patent protection. After the patent expires, others may manufacturer and sell the drug under their own name, or under the generic name.
* **LAWS REGULATING DRUG DEVELOPMENT, MARKETING, PRESCRIPTION AND USE**
  + **Federal laws** regulate the manufacture and sale of drugs in interstate commerce. These laws empower the FDA (Food and Drug Administration) to approve each drug for sale and advertising when the FDA is satisfied about its purity, safety, and effectiveness. Note that there is no requirement that the drug be shown to as effective as already-approved dugs, or to provide new or unique benefits.
  + An approved prescription drug may be dispensed only by the order of a licensed practitioner. [State laws determine who may prescribe drugs]. After a prescription drug has been in use long enough to establish a safe record, the drug may be evaluated by the FDA for sale as a non-prescription, or “over-the-counter” (OTC) drug. A different agency, the Drug Enforcement Agency (DEA), has additional authority over "Controlled Substances"; i.e., drugs that are likely to be abused, and be associated with addiction or dependence.
* **DRUG APPROVAL PROCESS**
  + FDA regulations mandate the following steps for any candidate drug:
    - Preclinical evaluation of safety and efficacy in animals. Typically 3-4 years, and using multiple species. Goals are to provide evidence of effectiveness, data on appropriate human dose for initial testing, information about mechanism of action and pharmacokinetic characteristics, acute and chronic toxicity, carcinogenesis and mutagenesis.
  + **IND (Investigational New Drug).** With results of the preclinical studies, an IND application is filed to get permission for the following **clinical studies.**
    - Phase I clinical trial. Done with a small number of healthy volunteers, typically 20-100. Goals are to determine the safe dose range in man and to provide pharmacokinetic data.
    - Phase II clinical trial. Conducted on a limited number of patients to determine safety and probable efficacy. Typically 100-200 patients, often single-blind design, typically in specialized clinical testing centers.
    - Phase III clinical trial. If the drug gets through Phase II, the studies are repeated with a large population of patients (1,000 - 6,000). Usually 2-4 years, double-blind, controlled trials, usually at multiple sites.
  + **NDA (New Drug Application)**. With all of the above data, the sponsor may file a NDA for approval by the FDA. This review is usually about ó to 3 years, and the FDA may require additional testing. Approval of the NDA marks the appearance of the drug in the marketplace. Though it is approved for a specific use, except under very unusual circumstances, the physician is under no legal obligation to limit the use of the drug to this specific use. With approval for manufacturing and sale, FDA must also approve the claims (advertisements) of the sponsor regarding safety and efficacy.
    - Phase IV - monitoring. FDA also requires post-marketing monitoring by the manufacturer to detect "unexpected" toxic reactions. All physicians can (should) report unexpected problems. Based on these, approval may be withdrawn, or other changes made.
  + On average, it takes about 10 years for a drug to go from preclinical testing to market. About 5 of 4,000 drugs subjected to preclinical testing make it to human testing; only one of these 5 is approved by FDA, at an average cost of more than $800 million/drug.
* **INTERACTIONS BETWEEN PRACTITIONERS AND THE PHARMACEUTICAL INDUSTRY**
  + The pharmaceutical industry needs physicians (and their patients) for Phase II and III studies, and is willing to pay. There have been a few notable instances made public of physicians who have gotten involved in practices that are, or which give the appearance of misconduct. The pharmaceutical industry has the goal of making a profit. They need to persuade you to prescribe their drug. The mechanisms used, and the ethics of some practices, are topics of much discussion. Many physicians do not feel that they, personally, are influenced by gifts, free lunches for their office staff, continuing education programs at golf resorts, free samples for patients, etc. Published evidence shows they are mistaken (see Brennan et al, JAMA, 295:429-433, 2006; this source can point you to several useful publications). Moreover, there is concern that physicians are unduly influenced to the detriment of the public.
  + The industry spends a huge amount on “education”, including interactions between the physician and educational representative (“sales rep”). Many are of the opinion that the main objective is not education, but to get the doctor to prescribe the particular drug, regardless of its relative benefits and risks as compared to alternate treatments.
  + Several physicians and groups of physicians have advocated taking NO gifts, samples, or other materials from the pharmaceutical industry, and not to meet with their “educational representatives”